<u>FDA Executive Summary</u>

Prepared for the
December 11, 2013 meeting of the
Circulatory System Devices Panel

P130013

Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy

<u>INTRODUCTION</u>

This is the <u>FDA Executive Summary</u> for a first-of-a-kind transcatheter left atrial appendage closure device, the Boston Scientific WATCHMAN Left Atrial Appendage Closure (LAAC) Therapy (WATCHMAN device), indicated for reducing the risk of stroke and systemic embolism in warfarin-eligible patients with non-valvular atrial fibrillation. Feasibility and pivotal studies were conducted between September 12, 2003 and June 28, 2012 under IDE G020312.

A PMA submission (P080022) for marketing approval of this device containing the results of the PROTECT AF pivotal study was previously reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) and presented to the Circulatory System Devices Panel on April 23, 2009. The Panel voted 7 to 5 in favor of "Approval with Conditions." Although FDA recognized that the PROTECT AF trial showed potential clinical benefit of the WATCHMAN device, the Agency concluded that the study results did not demonstrate a reasonable assurance of device safety and effectiveness. In reaching this decision, the FDA considered the following major issues, which led to challenges in the interpretation of the PROTECT AF trial results:

- Substantial enrollment of $CHADS_2$ = 1 subjects (31%), who were eligible for enrollment per the study protocol but may have been acceptable candidates for aspirin therapy rather than anticoagulation;
- Concomitant use of chronic clopidogrel therapy in both study groups (51% of follow-up time in device subjects and 16% of follow-up time in control subjects); and
- Safety concerns regarding serious peri-procedural WATCHMAN device implantation adverse events including pericardial effusion and air embolism.

A Not Approvable letter was issued on March 11, 2010. Subsequently, FDA worked collaboratively with the sponsor to design a new clinical study (the PREVAIL trial) to address the limitations of the PROTECT AF data. Further, because FDA recognized value in the safety and effectiveness information captured in the PROTECT AF trial, the sponsor and FDA developed a Bayesian study for PREVAIL in which a portion of the PROTECT AF data would be used as an informative prior. This study design methodology allowed the sponsor to efficiently collect additional safety and effectiveness data on the WATCHMAN device in a least burdensome manner. In addition to new data collected in PREVAIL, continued follow-up of PROTECT AF subjects was collected to provide critical insights into long-term device safety and effectiveness.

The results of PREVAIL and additional long-term follow-up data from PROTECT AF have been reviewed by the FDA under Premarket Approval (PMA) application P130013, which is the subject of this Advisory Panel meeting. This memorandum will summarize the FDA's review of the submitted PMA application, highlighting areas for which we are seeking the Panel's expertise and recommendations. Panel input is especially important on the proposed indications for use, the results of the PREVAIL trial, long-term follow-up data from the PROTECT AF trial, and the proposed post-approval study.

At the conclusion of the Panel's review and discussion of the data presented, the Agency will ask for recommendations regarding whether or not the data demonstrate a reasonable assurance of device safety and effectiveness, and whether the probable benefits of the device outweigh the probable risks. It is critical that Advisory Panel members review the totality of data in making these determinations as each component of the dataset has strengths and limitations.

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1 PROPOSED INDICATIONS FOR USE

The sponsor has proposed the following Indication for Use:

"The WATCHMAN Left Atrial Appendage Closure (LAAC) Therapy is intended to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy, but, for whom the risks posed by long term warfarin therapy outweigh the benefits."

FDA Comment: The Panel will be asked to comment on whether the proposed Indications for Use statement is appropriate.

2 DEVICE DESCRIPTION

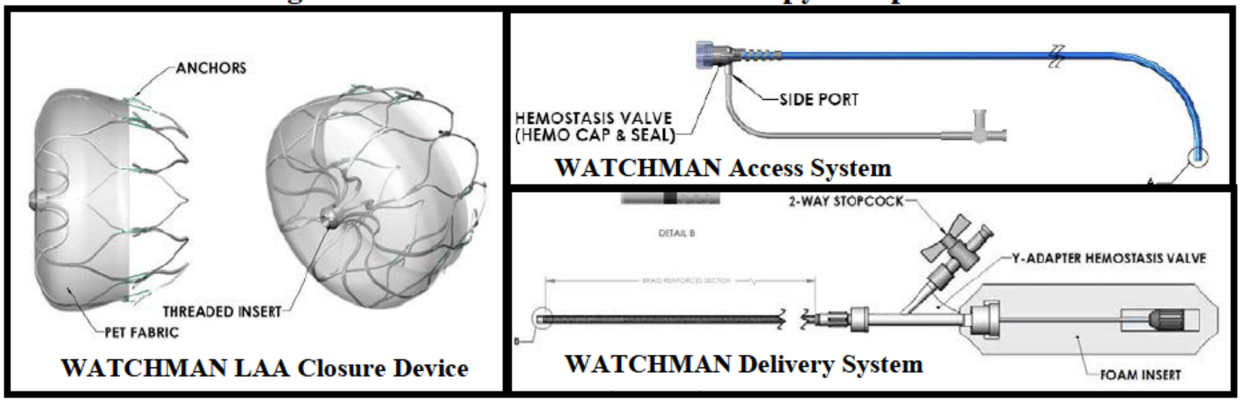
The WATCHMAN device consists of three components: (1) the WATCHMAN LAA Closure Device; (2) the WATCHMAN Delivery System, and (3) the WATCHMAN Access System (see Figure 1).

The WATCHMAN LAA Closure Device is a self-expanding nitinol structure covered by a porous polyethylene terephthalate (PET) membrane on the proximal face. The Access System and Delivery System allow for femoral venous access and provide a means to cross into the left atrium via the inter-atrial septum.

The WATCHMAN LAA Closure Device is packaged preloaded into the WATCHMAN Delivery System and is manufactured in five sizes corresponding to the maximum device diameter (21 mm, 24 mm, 27 mm, 30 mm, and 33 mm). The device size is intended to correspond to the maximum LAA ostium diameter. Per the Instructions for Use, device selection should be based on accurate LAA measurements obtained using fluoroscopy and transesophageal echocardiography (TEE) from multiple angles.

Following use of a standard transseptal access system to cross the atrial septum, the 12 French (Fr) Delivery System is placed through a 14 Fr Access Sheath. The Access Sheath comes in three configurations: the single curve (90 degree angle), double curve, and anterior curve distal tip. Upon proper positioning, the device is deployed by unscrewing the core wire from the permanent implant microscrew attachment.

Figure 1: WATCHMAN LAAC Therapy Components



3 BACKGROUND INFORMATION AND REGULATORY HISTORY

Atrial fibrillation (AF) is a clinically important arrhythmia with an estimated prevalence of approximately 1% in the U.S., and the development of AF is associated with increased age and the presence of underlying heart disease.[1] In addition to interventions targeted to heart rate and rhythm control, the treatment of AF involves the prevention of ischemic stroke and systemic embolism in patients with paroxysmal, persistent, or permanent AF. The etiology of stroke, with an estimated incidence of 3 to 5% per year[2] is presumed, in most part, to be related to the embolization of left atrial appendage thrombus. In clinical practice, the $CHADS_2$ and CHA_2DS_2 - VASc[3] scoring systems provide risk stratification data on the likelihood of stroke or systemic embolism and are used to guide therapy (anticoagulation or aspirin).

In patients eligible for anticoagulation therapy, warfarin is the historical standard of care. The effectiveness of warfarin to prevent ischemic stroke and systemic embolism is directly related to maintaining a therapeutic INR. A subtherapeutic INR increases the risk of ischemic stroke, and a supratherapeutic INR is associated with an increased risk of major bleeding complications. Achieving a therapeutic INR can be difficult in some patients as it requires patient compliance with regular monitoring and is affected by diet and concomitant medication use. Over the last three years, three novel anticoagulants (NOACs: dabigatran, rivaroxaban, and apixaban) have been approved by FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Each of the NOACs has a different benefit-risk profile versus warfarin as shown in large global randomized trials.[4,5,6] For example, dabigatran (150 mg twice

[1] Go AS, Hylek EM. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285(18):2370-5.
[2] Wolf PA, Kannel WB. Duration of atrial fibrillation and imminence of stroke: the Framingham study. Stroke 1983;14(5):664-7.
[3] Lip GY, Nieuwlaat R, Pisters R. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. Chest. 137 2010:263-272.
[4] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151

per day) and apixaban were shown to be superior and rivaroxaban was shown to be non-inferior to warfarin for the endpoint of stroke and systemic embolism. Both dabigatran and apixaban were associated with a reduction of the rate of hemorrhagic stroke vs. warfarin, and apixaban was associated with a reduced rate of major bleeding vs. warfarin (major bleeding rates were similar to warfarin with dabigatran and rivaroxaban). However, the NOACs are costly, require compliance with once or twice per day dosing, and lack a readily available agent to reverse their anticoagulant effect. Physician experience with these new anticoagulants is evolving, but it is relatively limited vs. warfarin. A data analysis from the American College of Cardiology's PINNACLE Registry showed that of patients receiving oral anticoagulation for atrial fibrillation, 87.4% were treated with warfarin in 2011 and 12.6% were prescribed one of the NOACs.[7] In a province-wide analysis of prescribing patterns in Ontario between October 2010 and September 2012, prescriptions for NOACs increased >20-fold, but still comprised only 21.1% of all anticoagulation therapy prescriptions.[8] Although use of the NOACs in the U.S. is increasing, warfarin remains a widely used and acceptable therapy to reduce the risk of ischemic stroke and systemic embolism in patients with non-valvular AF. Because of the challenges in maintaining a stable therapeutic INR in some warfarin patients, as well as individual physician and patient preference to avoid anticoagulation therapy altogether,[9] alternatives to anticoagulation have been developed.

The WATCHMAN device was originally manufactured by Atritech, Inc., and Boston Scientific acquired Atritech, Inc., in March 2011. Under Investigational Device Exemption (IDE) G020312, the PILOT feasibility study was conditionally approved on September 12, 2003 and the PROTECT AF pivotal clinical trial was conditionally approved on November 3, 2004. The PROTECT AF study was designed as a prospective, randomized, controlled, multicenter clinical trial to evaluate the safety and effectiveness of the WATCHMAN device.

The results from the PROTECT AF study were submitted to the FDA as part of PMA P080022, which was presented to the Circulatory System Devices Panel on April 23, 2009 (see Appendix A for a summary of the PROTECT AF study design and previous primary endpoint results). Based on the data from the PROTECT AF trial, the Panel concluded that short-term effectiveness of the WATCHMAN device had been demonstrated. However, the Panel believed that there was insufficient evidence to support long-term device effectiveness. Although the Panel voted 7 to 5 in favor of "Approval with Conditions," P080022 was deemed Not Approvable by the FDA. In the Not Approvable letter issued on March 10, 2010, FDA requested that the sponsor conduct a new prospective trial of the WATCHMAN device, citing the following concerns:

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[5] Patel MR, Mahaffey KW Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-891.
[6] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.
[7] PINNACLE-AF Registry Suggests Slow Uptake of New Anticoagulants. *Medscape*. August 17, 2012.
[8] Xu Y, et al. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. CMAJ Open 2013; 1(3): E115-E119.
[9] Connolly SJ, Eikelboom J. Challenges of Establishing New Antithrombotic Therapies in AF. Circulation. 2007;116(4):449-455.

"FDA believes that there are issues with the conduct and execution of the PROTECT AF trial that preclude assessment of device safety and effectiveness. The most significant of these issues cannot be adequately addressed with longer term patient follow-up data or additional registry data. In particular, assessment of device efficacy is precluded in light of the variable concomitant antithrombotic medication use in both study arms. This medication use confounds interpretation of device efficacy and the contributing effect of the device, if any. This confounding factor is further complicated by a non-inferiority trial design which relies on the assumption that study groups receive their assigned treatment and unfortunately, in the case of the PROTECT AF trial, a substantial portion of both control and Watchman patients did not receive their assigned treatment. Furthermore, the majority of Watchman patients in this non-inferiority trial who did not receive their assigned treatment received the control treatment. It is also notable that the composite endpoint is difficult to interpret in that the hemorrhagic stroke rate in the control arm is greater than expected, either as a result of the wide confidence interval given the small trial size or unknown differences in patient population or treatment strategies compared to similar published trials. For these reasons, the prospective intent-to-treat statistical analysis and the ad hoc analyses are not instructive regarding device effectiveness. Device safety issues, not included in the primary endpoint unless leading to a primary efficacy event, are also not insignificant (e.g., device thrombus, pericardial perforations, explantation) and incrementally contribute to concerns about potential adverse outcomes with device. As indicated in our meeting of January 29, 2010, FDA is willing to work collaboratively with you to develop a subsequent trial that could provide adequate evidence of safety and effectiveness. Such a trial could be designed taking into account the data and information gained from PROTECT AF to support the originally proposed indication."

Subsequently, FDA worked interactively with the sponsor on the design of a new trial to gather additional safety and effectiveness data on the WATCHMAN device and address the concerns discussed by the Panel. In July 2010, FDA conditionally approved the PREVAIL trial which is a prospective, randomized, controlled, multicenter clinical trial that utilizes a Bayesian design. FDA recognized that while the existing data from PROTECT AF were not adequate to provide a reasonable assurance of device safety and effectiveness, there was value in the information captured in the PROTECT AF trial. Therefore, the PREVAIL study was designed to borrow strength from PROTECT AF by incorporating a portion of the PROTECT AF data into a Bayesian statistical analysis plan, while simultaneously addressing the limitations of the PROTECT AF study.

The specific limitations of the PROTECT AF study that PREVAIL was designed to address are as follows:

1. Patient Population: PROTECT AF permitted enrollment of subjects with $CHADS_2$ score ≥ 1, and $CHADS_2$ score = 1 subjects accounted for 33.7% of device subjects and 27% of control subjects. Professional society guidelines[10] available at the time of PROTECT AF indicated that

[10] Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. JACC 2006;48:e149-246.

$CHADS_2$ score = 1 subjects could be adequately treated with aspirin rather than necessarily requiring oral anticoagulation therapy. Inclusion of $CHADS_2$ score =1 subjects who are considered eligible for aspirin therapy alone was problematic because these lower risk subjects are not truly representative of a warfarin-eligible patient population for whom a LAA occlusion device would likely be considered.

> **FDA Comment**: PREVAIL enrolled higher risk subjects than PROTECT AF by limiting inclusion to subjects with $CHADS_2$ score ≥ 2. $CHADS_2$ score = 1 subjects were eligible for PREVAIL if additional stroke risk factors were present and warfarin therapy recommended according to ACC/AHA/ESC 2006 Guidelines[10].

2. Adjunctive Antiplatelet Therapy: PROTECT AF allowed subjects in both treatment groups to be on chronic aspirin and/or clopidogrel therapy at the discretion of the treating physician. In addition, per protocol, subjects in the device group were to be on aspirin throughout the duration of the study and clopidogrel through six months if they discontinued warfarin at day 45. The percentage of follow-up duration that subjects were on clopidogrel was higher in the device group compared to the control group (51% versus 16%). Similarly, the percentage of follow-up duration that subjects were on aspirin was higher in the device group (91%) versus the control group (54%).

Data were not available on the number of events occurring with or without one or two antiplatelet medications. Some control subjects who had endpoint events were on a combination of warfarin, clopidogrel, and/or aspirin. It was difficult to assess the contribution of the use of concomitant antiplatelet drugs to protection from ischemic complications (such as ischemic stroke) vs. a contributing factor to bleeding complications (such as hemorrhagic stroke). Other stroke trials, such as WARSS[11] have shown a positive, albeit limited effect of antiplatelet medications. Therefore, it was unclear whether some of the outcome differences between the device and control groups in PROTECT AF could be explained by the use of antiplatelet drugs.

> **FDA Comment**: PREVAIL excluded subjects indicated for chronic clopidogrel therapy to avoid this potential confounding issue. However, it is important to note that per the PREVAIL protocol, subjects in the device group who discontinued warfarin if the 45-day TEE showed LAA occlusion were to be treated with clopidogrel through six months after device implantation.

3. Warfarin Compliance: Warfarin use and maintenance of a therapeutic INR in PROTECT AF was a confounding issue for both the device and control treatment groups; subjects had INR measurements in the therapeutic range (between 2.0 and 3.0) approximately one-half of the time during protocol-required warfarin administration (46.3% of the time in the device group and 54.2% of the time in the control group). In addition, a substantial number of subjects in both treatment groups did not receive their intended treatment with respect to warfarin therapy. In the

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[11] Mohr et al., A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345(20):1441-51.

device group, 26.4% (117/442) of subjects remained on warfarin beyond the intended short-term duration of 45 days after device implantation. Reasons for continuation of initial warfarin therapy included 12% (55/442) of subjects who did not have the device successfully implanted and an additional combined 14% (62/442) of subjects who remained on therapy >60 days for reasons such as flow around the device at 45 days, physician preference, device explant or embolization, TEE not performed, and thrombus on the device. In the control group, 27.3% (65/238) of subjects discontinued or interrupted warfarin therapy during follow-up.

Although it is recognized that compliance with warfarin use and monitoring can be difficult in real world medical practice, suboptimal rates of maintaining a therapeutic INR in PROTECT AF, combined with a substantial numbers of:

(1) device subjects who continued warfarin; and

(2) control subjects who discontinued or interrupted warfarin

made it challenging to evaluate the safety and effectiveness of the WATCHMAN device vs. warfarin therapy.

> **FDA Comment**: While the issue of warfarin compliance was not specifically addressed in the PREVAIL protocol, the sponsor committed to improved enhanced monitoring of warfarin use in PREVAIL to ensure adequate compliance and improved INR control and minimize this confounding issue.

4. Non-inferiority Margin: In PROTECT AF, the non-inferiority margin for the event rate ratio for the primary effectiveness endpoint of stroke (ischemic or hemorrhagic), systemic embolism, and cardiovascular/unexplained death was set at 2.0. This margin allowed for a reasonably-sized clinical trial; however, it is larger than margins typically used in anticoagulation drug trials and meant that the WATCHMAN device could be found non-inferior to warfarin with an event rate up to 2 times that in the control group.

> **FDA Comment**: To increase scientific rigor, the non-inferiority margin for the event rate ratio for the primary effectiveness endpoint in PREVAIL was set at 1.75. To increase clinical trial efficiency, FDA and the sponsor agreed to leverage a portion of the data from PROTECT AF in a Bayesian statistical analysis of PREVAIL to allow this non-inferiority margin to be tested with a smaller number of newly enrolled subjects.

5. Proof of Concept of LAA occlusion for Prevention of Ischemic Stroke: The WATCHMAN device is intended to reduce the risk of ischemic stroke by preventing the embolization of thrombus from the left atrial appendage (LAA). The ischemic stroke rate in PROTECT AF numerically favored the control group (3.0% in the device group vs. 2.0% in the control group). When considering the WATCHMAN's intended mechanism of ischemic stroke prevention (occlusion of the LAA), however, of the 14 ischemic strokes in the device group, there was 1 pre-procedure event and 5 procedural events (3 due to air embolism). Furthermore, the primary effectiveness endpoint in PROTECT AF included both ischemic and hemorrhagic strokes; there were 6 hemorrhagic strokes in the control group (corresponding to a 2.5% hemorrhagic stroke rate) in PROTECT AF, which represented a higher rate than observed in contemporary AF anticoagulation clinical trials. Taken together, the peri-procedural ischemic strokes in the

WATCHMAN group, and the unexpectedly high rate of hemorrhagic strokes in the control group among the primary endpoint events, made it difficult to conclude that device occlusion of the LAA was comparable to warfarin in reducing the risk of stroke.

FDA Comment: The second primary endpoint included in the PREVAIL trial was developed to compare the rate of ischemic stroke and systemic embolism (beyond the first 7 days post-randomization to exclude peri-procedural events). This endpoint addresses whether, beyond the peri-procedural period, the WATCHMAN may be an acceptable treatment alternative to warfarin in reducing the risk of ischemic stroke and systemic embolism.

6. Acute Safety Events: In PROTECT AF, a majority (27/48, 56%) of primary safety events in the device group occurred on the day of the procedure. These 27 events consisted of 17 serious pericardial effusions, 5 ischemic strokes, 1 device embolization and 4 other events. Of the 5 ischemic strokes, 3 were related to air embolism during the procedure. Of the remaining 21 events, 9 occurred within 7 days of the procedure and 12 occurred more than 7 days post-procedure. In the clinical protocol, there was no pre-specified hypothesis test for procedural safety.

FDA Comment: Because of concerns regarding the rate of peri-procedural safety events observed in PROTECT AF, PREVAIL also included a co-primary composite endpoint consisting of the rate of occurrence of all-cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair, occurring between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later.

7. Procedural Learning Curve: In evaluating the rate of pericardial effusion in the WATCHMAN group of PROTECT AF, there were more effusions in the first half of enrolled subjects (n = 17) compared to the second half of enrolled subjects (n = 12). In addition, the rate of pericardial effusions observed in early subjects (first three subjects enrolled at a site) was higher (7.2%) compared to later subjects (subject 4 and onward, 4.7%). Furthermore, the number of device recaptures observed in PROTECT AF was greater in the first half of enrolled subjects (1.8 recaptures per subject) compared to the second half (1.5 recaptures per subject) of the study. Among early subjects, 49% had zero recaptures compared to 61% with zero recaptures in the later subject cohort. These findings suggested important operator learning curve issues over the course of the study and raised concerns about the ability of new operators to safety implant the WATCHMAN device.

FDA Comment: To provide an evaluation of the procedural learning curve, PREVAIL required that at least 20% of subjects were to be implanted at new investigational sites, and at least 25% of subjects were to be implanted by new operators at either new or experienced sites.

Leveraging Data To Assess WATCHMAN Safety and Effectiveness: Despite limitations, the data from PROTECT AF were still informative. The sponsor and FDA agreed to incorporate a portion of PROTECT AF data into the PREVAIL analyses. In addition to collecting new data in PREVAIL, the sponsor also continued to follow subjects enrolled in PROTECT AF and the Continued Access to PROTECT AF (CAP) Registry to gather additional data on procedural safety and long-term safety and effectiveness.

FDA Comment: To build on the prior information from PROTECT AF, the primary effectiveness endpoint in PREVAIL was the same as PROTECT AF. Additionally, some data from PROTECT AF and CAP were used as prior information in the statistical analysis of the primary endpoints in PREVAIL. For details of the Bayesian trial plan, see Section 5.2 and Appendix C. Although FDA determined that the limitations of PROTECT AF precluded earlier approval of the WATCHMAN device, additional follow-up data from PROTECT AF and the CAP registry, in combination with the new data from PREVAIL, should be considered in evaluating the safety and effectiveness of the device.

Current PMA: PMA P130013 was filed on June 10, 2013 and includes the results of the PREVAIL clinical trial and additional follow-up from the PROTECT AF study and CAP registry. The design and manufacturing process for the current WATCHMAN device are essentially unchanged from the previous PMA submission (P080022), and most of the pre-clinical data has been leveraged from the prior PMA. Like the prior PMA submission of the PROTECT AF trial, the PREVAIL trial PMA submission was granted priority review status, since the WATCHMAN device is intended to treat a life-threatening or irreversibly debilitating disease or condition (i.e., stroke), and the device represents a potential breakthrough technology for patients with non-valvular atrial fibrillation, a clinically significant and common medical condition.

4 PRECLINICAL STUDIES

4.1 BENCH STUDIES

The sponsor conducted *in vitro* performance and characterization studies of the WATCHMAN device. The bench testing submitted and reviewed in the previous PMA submission was incorporated by reference into the current PMA. In addition, new bench data were submitted to resolve the issues outlined in the Not Approvable letter. The bench testing conducted by the sponsor is summarized below:

- Test results demonstrated that the device is compliant with FDA recognized international standards for biocompatibility.
- Packaging and sterilization processes were validated according to FDA-recognized international standards.
- The WATCHMAN LAA Closure Device (implant) was evaluated for MRI compatibility.
- FDA comprehensively reviewed pre-clinical bench testing performed under challenging conditions to verify the design of all components of the WATCHMAN device.

- Testing included fatigue (10 years of simulated use) and corrosion evaluation of the nitinol implant frame.
- The results of the bench testing supported device safety in the anticipated clinical environment for the intended patient population.

FDA Comment: All outstanding deficiencies related to pre-clinical bench testing have been resolved. FDA has no remaining concerns regarding the pre-clinical bench testing.

4.2 ANIMAL STUDIES

No new animal testing data were submitted in this PMA. The animal study data that were submitted and reviewed in the previous PMA submission were incorporated by reference into the present PMA.

FDA Comment: FDA has no concerns regarding the pre-clinical animal testing.

5 PREVAIL STUDY DESIGN

Study Name: Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device in Patients with Atrial Fibrillation versus Long Term Warfarin Therapy (PREVAIL)

Study Objective: To demonstrate the safety and effectiveness of the WATCHMAN device for the prevention of ischemic stroke and systemic thromboembolism in subjects with non-valvular atrial fibrillation who require treatment for potential thrombus formation and who are eligible for warfarin therapy.

Study Design: Prospective, multicenter, randomized study comparing WATCHMAN device implantation plus short term (45-days) warfarin therapy (device group) compared to warfarin therapy (control group).

Subjects and Investigational Sites: A total of 461 subjects were enrolled at 41 US sites. This total included 269 randomized to the device group, 138 randomized to the warfarin control group, and 54 roll-in subjects. There was a requirement to enroll at least 20% of randomized subjects from new centers and at least 25% of randomized subjects by new operators at either new or experienced sites.

Randomization Scheme: A 2:1 randomization ratio (Device:Control) with stratification by center.

Treatment Groups:

Device Group - Short Term (45-day, window ≤60 days) Warfarin Therapy: The WATCHMAN device was implanted into the LAA via atrial transseptal access. Subjects were treated with adjusted dose warfarin plus 81 mg aspirin. At 45 days post-procedure, if the TEE demonstrated adequate LAA occlusion, warfarin therapy could be discontinued, with continuation of warfarin at the discretion of the treating physician. Subjects who discontinued warfarin were treated with 325 mg aspirin plus 75 mg clopidogrel. Subjects remained on clopidogrel through 6 months post-device implantation, and 325 mg aspirin was continued indefinitely.

Control Group - Anticoagulation Therapy: Either initiation or continuation of warfarin therapy with a target INR of 2.0-3.0 for the duration of the trial.

Follow-up Schedule: All enrolled subjects in both groups were required to receive follow-up assessments according to the schedule in Table 1.

Table 1: PREVAIL Follow-Up Requirements

Evaluation Requirements	**Baseline & Procedure**			**Follow-Up**					
	Screen	Implant	Post	45 Day Visit	6 Month Visit	9 Month Telephone	12 Month Visit	18 month 30 month Telephone	Annual Visits
Informed Consent	X								
Assess Inclusion/Exclusion	X								
Medical History	X								
Pregnancy Test[a]	X								
TTE	X								
TEE	X[b]	Device Group		Device Group	Device Group		Device Group		
Brain Imaging (CT/MRI)[d]	X[c]		As required[d]	As required[d]	As required[d]	As required[d]	As required[d]	As required[d]	As required[d]
INR Monitoring[e]	X		X	X	X	X	X	X	X
Serum Creatinine, Platelet count, Hgb	X								
Review Medication Regimen	X	Device Group	X	X	X	X	X	X	X
Vital Signs	X			X	X		X		X
Neurologist Assessment[f]	X						X		
NIH Stroke Scale	X			X	X		X		X
Barthel Index / Modified Rankin	X			X	X	X	X	X	X
Adverse Event Monitoring	X	Device Group	X	X	X	X	X	X	X

a For women of childbearing potential only
b Within 2 days prior to randomization
c Obtain at baseline or within 30 days prior to study enrollment if subject had prior stroke or TIA
d Brain MRI or CT required if subject suffers stroke or TIA
e INR monitoring is required at least every 28 days for all patients through the 45-day visit and for all subjects on warfarin therapy throughout the duration of the study
f Neurology consultation required at baseline and 12 months and if a subject experiences a stroke or TIA throughout the duration of the study

5.1 *INCLUSION/EXCLUSION CRITERIA*

Selected Inclusion Criteria

1. 18 years of age or older
2. Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
3. Eligible for long-term warfarin therapy
4. Eligible to come off warfarin therapy if the LAA is sealed (i.e., the subject has no other conditions that would require long-term warfarin therapy per standard medical practice)
5. $CHADS_2$ score of 2 or greater; subjects with a $CHADS_2$ score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation):
   - The subject is a female age 75 or older
   - The subject has a baseline LVEF ≥30 and <35%
   - The subject is age 65-74 and has diabetes or coronary artery disease
   - The subject is age 65 or greater and has documented congestive heart failure

Selected Exclusion Criteria

Clinical (pre-echocardiography) Exclusion Criteria

1. Requirement for long-term warfarin therapy (i.e., even if the device is implanted, the subject would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, any of the following excluded a subject:
   - Thrombosis occurring at a young age (<40 years old)
   - Idiopathic or recurrent venous thromboembolism (VTE)
   - Thrombosis at an unusual site (e.g., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins)
   - Family history of VTE or an inherited prothrombotic disorder
   - Recurrence or extension of thrombosis while adequately anticoagulated
2. Subject is contraindicated for warfarin therapy or cannot tolerate long-term warfarin therapy
3. Subject is contraindicated or allergic to aspirin
4. Subject is indicated for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment
5. Stroke, TIA, or MI within the 90 days prior to enrollment
6. New York Heart Association Class IV congestive heart failure
7. Symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient symptoms or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy, enrollment permitted if there was <50% stenosis
8. Subject's AF is defined by a single occurrence of AF
9. Subject had a transient case of AF (e.g., secondary to CABG or interventional procedure)
10. Resting heart rate > 110 beats per minute

Echocardiographic Exclusion Criteria (as assessed by TTE and TEE)

1. LVEF <30%
2. Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to device implant
3. Pericardial effusion >2mm
4. High risk patent foramen ovale, defined as an atrial septal aneurysm (excursion > 15 mm or length >15mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
5. Significant mitral valve stenosis (i.e., MV area <1.5 cm^2)
6. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch
7. Cardiac tumor

5.2 ENDPOINTS AND STATISTICAL ANALYSIS

There were three co-primary endpoints in this study, and a formal statistical hypothesis was prospectively established for each endpoint. The primary analysis was intent-to-treat (ITT), and was performed once all subjects had reached at least 6 months of follow-up.

A Bayesian approach based on a piecewise exponential model was used to evaluate the first and second primary endpoints. The number of events was assumed to follow a piecewise exponential distribution with parameter λ (hazard rate). The hazard rate is assumed constant within each of 4 time intervals (0 to ≤7 days, >7 to ≤60 days, >60-≤182 days, and >182 days), but differs between intervals, by event type and by treatment group. A conjugate beta-binomial model was used to evaluate the third primary endpoint. See Appendix B for a general summary of Bayesian statistics and Appendix C for a discussion of the Bayesian approach and model used in the PREVAIL trial.

A formal statistical hypothesis was prospectively established for each of the three co-primary endpoints:

1. First Primary Endpoint: **The occurrence of stroke (including ischemic and hemorrhagic stroke), cardiovascular death (cardiovascular and unexplained), and systemic embolism (18 month rates)**

A hypothesis to test for non-inferiority of the device group against the control group was specified in terms of the 18-month risk ratio, $rr_A = r_{D,A} / r_{C,A}$, where $r_{D,A}$ is a model-based rate of any event (ischemic/hemorrhagic stroke, cardiovascular/unexplained death, and systemic embolism) occurring within 18 months in the device group and $r_{C,A}$ is a model-based rate of any event occurring within 18 months in the control group (see Appendix C for the model description). The null and alternative hypotheses are as follows:

$$H_o: rr_A \geq 1.75$$
$$H_a: rr_A < 1.75$$

where the risk ratio upper bound is 1.75 (prospectively agreed to by the FDA and the sponsor).

Non-inferiority for the first primary endpoint would be met if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk ratio, $rr_A = r_{D,A} / r_{C,A}$, is less than 1.75.

2. Second Primary Endpoint: **The occurrence of late ischemic stroke and systemic embolism [8 days post-randomization and onward (i.e., excluding the first 7 days post-randomization), 18 month rates]**

A non-inferiority hypothesis was specified in terms of the 18-month risk ratio, $rr_T = r_{D,T}/r_{C,T}$, and risk difference, $rd_T = r_{D,T} - r_{C,T}$, where $r_{D,T}$ is a model-based rate of thrombotic event (ischemic stroke and systemic embolism) occurring within 18 months (excluding the first 7 days post randomization) in the device group and $r_{C,T}$ is a model-based rate of thrombotic event occurring within 18 months (excluding the first 7 days post randomization) in the control group (see Appendix C for the model description). The null and alternative hypotheses are as follows:

$$H_o: rr_T \geq 2.0 \text{ and } rd_T \geq 0.0275$$
$$H_a: rr_T < 2.0 \text{ or } rd_T < 0.0275$$

where the risk ratio upper bound of 2.0 and the risk difference upper bound of 0.0275 were prospectively agreed to by the FDA and the sponsor.

Non-inferiority for the second primary endpoint would be met if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk ratio, $rr_T = r_{D,T}/r_{C,T}$, is less than 2.0 **or** the upper bound of the equitailed 2-sided 95% credible interval for the 18-month risk difference, $rd_T = r_{D,T} - r_{C,T} < 0.0275$.

Non-inferiority for the WATCHMAN device vs. warfarin would be achieved if the non-inferiority criteria for both the first and second primary endpoints were met.

3. Third Primary Endpoint: **The occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair, occurring between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later.**

A statistical hypothesis was specified by comparing the percentage, p_o, of subjects experiencing one of these endpoint events with the performance goal (PG) of 2.67%. The sponsor derived the PG based on the expected rates of each endpoint component in the literature. The null and alternative hypotheses are as follows:

$$H_o: p_o \geq PG$$
$$H_a: p_o < PG$$

where the PG was set at 2.67% and was prospectively agreed to by the FDA and the sponsor.

Success for this endpoint was considered to have been achieved if the upper bound of the one-sided 95% credible interval for p_o is less than the PG of 2.67%.

5.3 PROTECT AF and CAP Historical Data

Pre-specified Bayesian statistical methods were used to integrate data from prior studies. Data collected in the PROTECT AF and the Continued Access to PROTECT AF (CAP) Registry studies were utilized as prior information in both the design and analysis of the PREVAIL study as follows:

- First and Second Primary Endpoints: Analyses were based on a piecewise exponential survival model assuming constant hazard rate within four pre-specified follow-up time intervals. The model assumptions, as well as prior distributions for the event rates in each interval, were based on PROTECT AF historical data as described in Appendix C. Importantly, prior PROTECT AF data included only subjects with the same $CHADS_2$ score inclusion criteria as the PREVAIL subjects to ensure similar patient populations. Specifically, only follow-up time and endpoint events experienced by subjects in PROTECT AF who would have met the PREVAIL enrollment criteria would be included in the analysis. In an attempt to incorporate PROTECT AF data yet avoid overly influencing the trial results, FDA and the sponsor agreed to use prior data in the analyses with a discounting weight of 50%. This means that the number of events and exposure time observed in PROTECT AF were down-weighted by 50% when using them as prior information in the final analysis of event rates.

- Third Primary Endpoint: Bayesian methods were used to incorporate the previously collected data from PROTECT AF trial and CAP registry through a prior distribution. As in the analysis of the first and second primary endpoints, these prior data only included those subjects with the same $CHADS_2$ score inclusion criteria as the PREVAIL subjects to ensure similar populations. There were 734 subjects in PROTECT AF and CAP with the same $CHADS_2$ inclusion criteria. There were 13 adverse events in these subjects, corresponding to a 1.8% event rate.

- A Bayesian adaptive design was used for sample size determination. The sample size was determined by assuming adequate statistical power, which was calculated based on the Bayesian statistical model for the first and second primary endpoints described above.

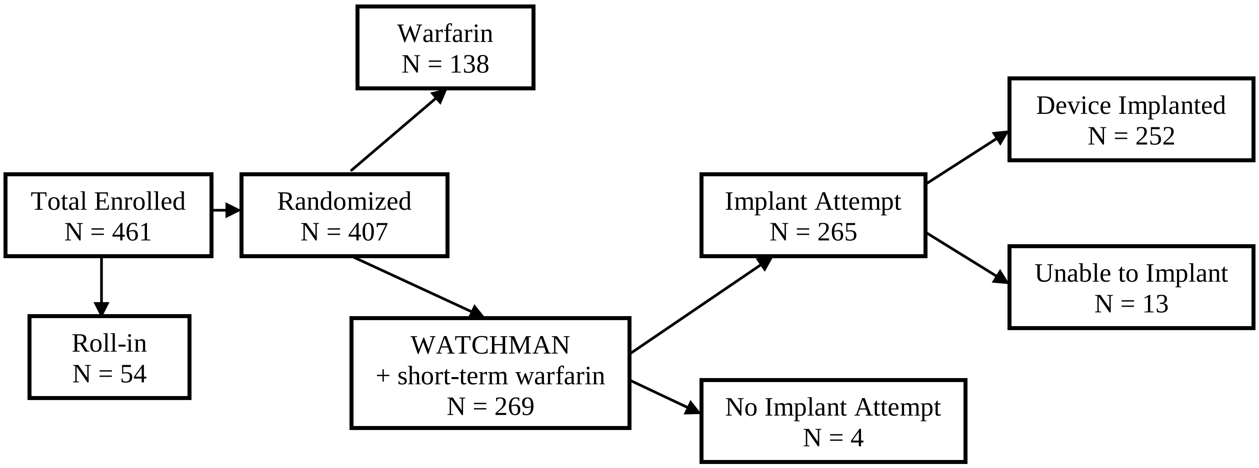
Additional analyses pre-specified in the statistical analysis plan included: analysis of event rates of each of the components of the first primary endpoint, individual adverse event rates, mortality rates, device- and procedure-related events, and a comparison of outcomes stratified by new vs. experienced operators/sites. In addition to the primary ITT analysis, the sponsor defined three additional secondary analysis populations: Post-Procedure, Per-Protocol #1, and Per Protocol #2. Descriptions of these secondary analysis groups are presented in the PREVAIL Results section.

6 PREVAIL STUDY RESULTS

6.1 SUBJECT ACCOUNTABILITY

A total of 461 subjects were enrolled at 41 U.S. sites. Total enrollment in PREVAIL included 269 subjects randomized to the device group, 138 subjects randomized to the control group, and 54 roll-in subjects. Subject accountability is summarized in Figure 2.

Figure 2: PREVAIL Subject Accountability



6.2 *SUBJECT DEMOGRAPHICS/BASELINE CHARACTERISTICS*

The device and control groups were well matched with respect to baseline demographic characteristics (two sample t-tests or chi-square tests, as appropriate, Table 2). The study population was predominately male (~70%) and overwhelmingly Caucasian (~94%).

Table 2: PREVAIL Baseline Demographics

Characteristic	Device N=269	Control N=138	P-value
Age (years) Mean ± SD (Min, Max)	74.0 ± 7.4 (50.0 ,94.0)	74.9 ± 7.2 (53.0 ,90.0)	0.260
Height (inches) Mean ± SD (Min, Max)	68.4 ± 4.3 (57.0 ,80.0)	68.5 ± 4.0 (57.0 ,78.0)	0.944
Weight (lbs) Mean ± SD (Min, Max)	196.3 ± 44.9 (106.0 ,333.0)	197.1 ± 43.3 (112.0 ,317.0)	0.851
Gender n/N (%)			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/Ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
Caucasian	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	

Values presented are mean ± standard deviation, n (minimum, maximum) or number of subjects/total number of subjects (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

With respect to baseline clinical characteristics (Table 3), there was a statistically significant difference in the percentage of subjects with a history of hypertension between the two groups (88.5% in the device group vs. 97.1% in the control group, p = 0.003).

Table 3: PREVAIL Baseline Risk Factors

Risk	Device N=269	Control N=138	P-value
$CHADS_2$ Score (Categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
$CHADS_2$ Score (Continuous)	2.6 ± 1.0 (269) (1.0 ,6.0)	2.6 ± 1.0 (138) (1.0 ,5.0)	0.838
CHF	63/269 (23.4%)	32/138 (23.2%)	0.958
History of Hypertension	238/269 (88.5%)	134/138 (97.1%)	0.003
Age ≥ 75	140/269 (52.0%)	78/138 (56.5%)	0.391
Diabetes	91/269 (33.8%)	41/138 (29.7%)	0.401
Previous TIA/Ischemic Stroke	74/269 (27.5%)	39/138 (28.3%)	0.873
AF Pattern			0.873
Paced	7/269 (2.6%)	5/138 (3.6%)	
Paroxysmal	131/269 (48.7%)	71/138 (51.4%)	
Permanent	42/269 (15.6%)	22/138 (15.9%)	
Persistent	85/269 (31.6%)	39/138 (28.3%)	
Unknown	4/269 (1.5%)	1/138 (0.7%)	
LVEF %	55.4 ± 10.0 (268) (30.0, 80.0)	56.0 ± 9.8 (137) (30.0, 77.0)	0.571
CHA_2DS_2 VASc Score (Categorical)			0.883
1	4/268 (1.5%)	1/137 (0.7%)	
2	27/268 (10.1%)	13/137 (9.5%)	
3	77/268 (28.7%)	41/137 (29.9%)	
4	92/268 (34.3%)	38/137 (27.7%)	
5	45/268 (16.8%)	31/137 (22.6%)	
6	18/268 (6.7%)	11/137 (8.0%)	
7	4/268 (1.5%)	2/137 (1.5%)	
8	1/268 (0.4%)	0/138 (0.0%)	
CHA_2DS_2 VASc Score (Continuous)	3.8 ± 1.2 (268) (1.0 ,8.0)	3.9 ± 1.2 (137) (1.0 ,7.0)	0.467

Values presented are mean ± standard deviation, n (minimum, maximum) or number of subjects/total number of subjects (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

FDA Comment: Compared to PROTECT AF (average $CHADS_2$ score of 2.2 in the device group and 2.3 in the control group), the average $CHADS_2$ score of PREVAIL subjects was higher (2.6 in both treatment groups), indicating a patient population at higher risk for stroke.

6.3 SUBJECT FOLLOW-UP

Compliance with follow-up visits ranged between 96% and 100% of expected and was similar between treatment groups (Table 4). The overall mean ± SD follow-up duration in PREVAIL was 11.8 ± 5.8 months for randomized subjects.

Table 4: PREVAIL Follow-up Visit Attendance

	Device	Control
Visit	**Attended/ Expected (%)**	**Attended/ Expected (%)**
45-Day	259/261 (99%)	132/137 (96%)
6-Month	239/241 (99%)	129/132 (98%)
9-Month	177/181 (98%)	89/93 (96%)
12-Month	142/144 (99%)	77/78 (99%)
18-Month	72/74 (97%)	39/39 (100%)
2 Years	9/9 (100%)	2/2 (100%)

FDA Comment: Note that only 113 of 407 (~28%) randomized subjects have reached or passed the window for their 18-month follow-up visit. The overall compliance with follow-up at each time interval, however, was very high.

6.4 *FIRST PRIMARY ENDPOINT RESULTS*

The primary analysis of the first primary endpoint was a comparison of the rate ratio of the composite 18-month rate of stroke, cardiovascular or unexplained death, and systemic embolism between the device and control groups in the ITT population. The 18-month rate represents a model-based rate of an event occurring within 18 months. More specifically, Bayesian inference was conducted to estimate this rate based on a piecewise exponential model and prior distributions constructed from the historical PROTECT AF trial data discounted 50% as described in Section 5.3 and Appendix C. Thus, the 18-month rate ratio is the mean of the 18-month rate ratio posterior distribution. The 18-month rate was 0.064 for the device group and 0.063 for the control group, and the 18-month rate ratio was 1.07 with a 95% credible interval of 0.57 to 1.89 (Table 5). The upper bound of the 95% credible interval for the 18-month rate ratio (1.89) is not lower than the non-inferiority margin of 1.75. Thus, the non-inferiority criterion *was not met* for the first primary endpoint based on the pre-specified hypothesis.

Table 5: PREVAIL First Primary Endpoint Results (ITT - PREVAIL and Historical PROTECT AF Data)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI Upper Bound < 1.75

CrI = credible interval

The Kaplan-Meier curve and estimates for freedom from the first primary endpoint based on ITT population (PREVAIL data only without the Bayesian prior) are included in Figure 3 and Table 6, respectively.

Figure 3: Kaplan-Meier Curve: Freedom From First Primary Endpoint Event (ITT - PREVAIL Data Only)

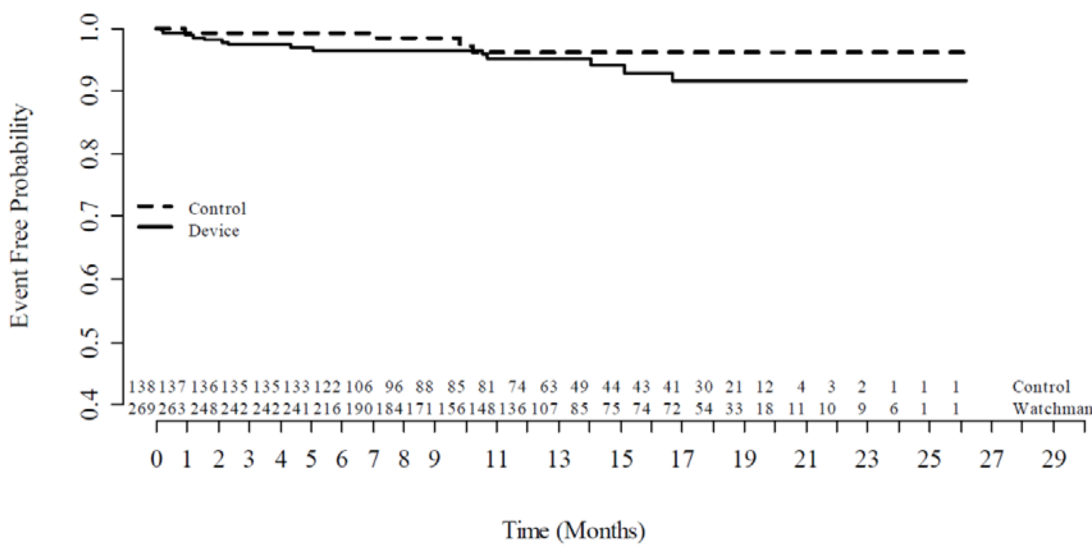


Table 6: Kaplan-Meier Estimates: Freedom from First Primary Endpoint (ITT - PREVAIL Data Only)

	Device Group			Control Group		
Time Point	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	2	2	99.2 (97.0, 99.8)	0	0	100.0 (100.0, 100.0)
45-days	2	4	98.5 (96.0, 99.4)	1	1	99.3 (95.0, 99.9)
6-months	5	9	96.5 (93.4, 98.2)	0	1	99.3 (95.0, 99.9)
1-year	2	11	95.3 (91.5, 97.4)	3	4	96.0 (89.6, 98.5)
2-year	3	14	91.6 (85.1, 95.3)	0	4	96.0 (89.6, 98.5)

Randomization Allocation (2 Device: 1 Control)

The sponsor analyzed the event rates of the individual first primary endpoint components (ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular or unexplained death) using the same model and Bayesian approach as was used for the composite first primary endpoint (Table 7).

Table 7: Bayesian Analysis Results: Components of First Primary Endpoint (ITT - PREVAIL and Historical PROTECT AF Data)

Component of First Primary Endpoint	Device Group 18-Month Rate (95% CrI)	Control Group 18-Month Rate (95% CrI)	Bayesian 18-Month Rate Ratio (95% CrI)
Stroke - Ischemic	0.03 (0.02, 0.05)	0.02 (0.01, 0.04)	2.05 (0.67, 5.27)
Stroke - Hemorrhagic	0.01 (0.00, 0.03)	0.03 (0.01, 0.06)	0.48 (0.13, 1.20)
Systemic Embolism	0.02 (0.01, 0.04)	0.02 (0.00, 0.04)	1.97 (0.52, 5.79)
Death (Cardiovascular or Unexplained)	0.03 (0.01, 0.04)	0.04 (0.02, 0.07)	0.68 (0.27, 1.43)

There were relatively few events in the PREVAIL trial contributing to this endpoint: 14 events in the device group and 4 events in the control group (Table 8). Of the 14 events in the device group, there were 5 ischemic strokes, 1 hemorrhagic stroke, 1 systemic embolism, and 7 cardiovascular or unexplained deaths. There were 3 cardiovascular or unexplained deaths and 1 ischemic stroke in the control group. Of note, the occurrence of ischemic stroke numerically favored the control group.

Cardiovascular or unexplained deaths accounted for at least 50% of the total first primary endpoint events (Table 8). Among the 7 deaths adjudicated as meeting the first primary endpoint definition in the WATCHMAN group, there were 5 sudden cardiac deaths and two deaths secondary to acute myocardial infarction. In the control group, all 3 deaths were sudden cardiac deaths. None of the deaths was causally linked to the WATCHMAN device, implantation procedure, or anticoagulant therapy.

The rates of the individual components of the first primary endpoint were also estimated using a Cox proportional hazards model, revealing that the rates of all components of the endpoint were numerically higher in the device group (Table 8).

Table 8: Cox Proportional Hazards Model Results: Components of First Primary Endpoint (ITT – PREVAIL data only)

Component of First Primary Endpoint	PREVAIL Device Group		PREVAIL Control Group	
	N Events	N Events/ Total Pt-Yrs (Rate)	N Events	N Events/ Total Pt-Yrs (Rate)
Stroke - Ischemic	5	5/257.1 (1.94)	1	1/140.1 (0.71)
Stroke - Hemorrhagic	1	1/259.0 (0.39)	0	0/140.8 (0.00)
Systemic Embolism	1	1/259.6 (0.39)	0	0/140.8 (0.00)
Death (Cardiovascular or Unexplained)	7	7/259.7 (2.70)	3	3/140.8 (2.13)

Rate per 100 pt-yrs = Event rate per 100 patient-years using a Cox proportional hazards model
Randomization Allocation (2 Device: 1 Control)

FDA Comment: Note that the rates calculated in Tables 6 and 8 include only data from PREVAIL subjects, while the results of the Bayesian analyses presented in Table 5 and Table 7 incorporate data from the PROTECT AF trial as prior information (discounted 50%). In addition, the results of the Bayesian analyses report model-based estimates of 18-month rates, but as noted above only 28% of subjects in PREVAIL have actually reached 18 months of follow-up. Model based assumptions are therefore important to consider. The Panel will be asked to comment on the clinical significance of the first primary endpoint results.

6.5 SECOND PRIMARY ENDPOINT RESULTS

The primary analysis of the second primary endpoint was a comparison of either the rate ratio or the rate difference of the composite 18-month rate of stroke and systemic embolism (excluding events occurring in the first 7 days) between the device and control groups. Like the first primary endpoint, the 18-month rate represents a model-based rate of an event occurring within 18 months. Bayesian inference was conducted to estimate this rate based on a piecewise exponential model and prior distributions constructed from the historical PROTECT AF trial data discounted 50% as described in Section 5.3 and Appendix C. Thus, the 18-month rate ratio is the mean of the 18-month rate ratio posterior distribution.

The 18-month rate was 0.0253 for the device group and 0.0200 for the control group (Table 9). The rate ratio was 1.6 with a 95% CrI of 0.5 to 4.2. The upper bound (4.2) of the 95% credible interval for the 18-month rate ratio is not lower than the non-inferiority margin of 2.0 (non-inferiority not met for the rate ratio). The rate difference is 0.0053 with a 95% credible interval of -0.0190 to 0.0273. The upper bound of 0.0273 is lower than the non-inferiority margin of 0.0275. Therefore, the non-inferiority criterion *was met* for the second primary endpoint based on the pre-specified hypothesis for the rate difference.

Table 9: PREVAIL Second Primary Endpoint Results (ITT)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0253	0.0200	1.6 (0.5, 4.2)	95% CrI Upper Bound < 2.0	0.0053 (-0.0190, 0.0273)	95% CrI Upper Bound < 0.0275

The Kaplan-Meier curve and estimates for freedom from the second primary endpoint based on ITT population (PREVAIL data only) are included in Figure 4 and Table 10, respectively.

Figure 4: Kaplan-Meier Curve: Freedom from Second Primary Endpoint Event (ITT - PREVAIL Data Only)

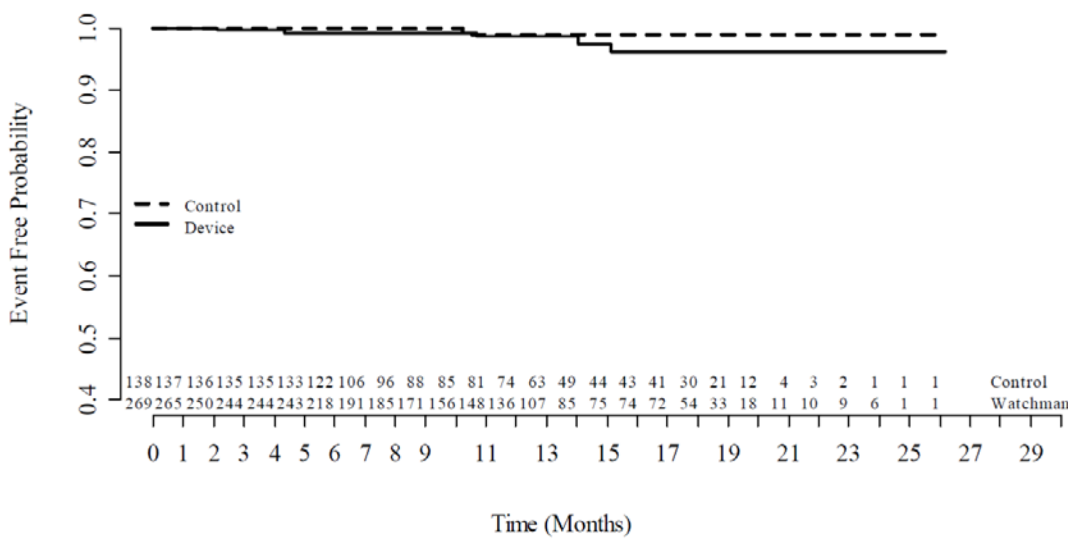


Table 10: Kaplan-Meier Estimates: Freedom from Second Primary Endpoint Event (ITT)

	Device			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
45-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
6-months	2	2	99.2 (96.8, 99.8)	0	0	100.0 (100.0, 100.0)
1-year	1	3	98.5 (95.4, 99.5)	1	1	98.8 (91.8, 99.8)
2-year	2	5	96.1 (89.8, 98.5)	0	1	98.8 (91.8, 99.8)

Randomization Allocation (2 Device: 1 Control)

Similar to the first primary endpoint, there were relatively few secondary endpoint events in the PREVAIL trial (5 in the device group, 1 in the control group) with the event rates numerically lower in the control group (Table 11).

Table 11: Second Primary Endpoint Events by Type (ITT)

Endpoint Event	Device Group			Control Group		
	N Events	% of Subjects	% of Endpoints	N Events	% of Subjects	% of Endpoints
Stroke-Ischemic	4	1.5	80.0	1	0.7	100.0
Systemic Embolism	1	0.4	20.0	0	0.0	0.0

Randomization Allocation (2 Device: 1 Control)

<u>FDA Comment</u>: The second primary endpoint is intended to measure device effectiveness (the ability of the device to prevent ischemic strokes and systemic embolism) without considering implantation procedure-related events. The event rates beyond the peri-procedural period numerically favored the control group, but it is difficult to draw definitive conclusions from such a small number of events. Like the first primary endpoint, note that the Bayesian analyses presented in Table 9 includes data from PROTECT AF and CAP as prior information (discounted 50%). With this approach, the Bayesian model reports a model-based estimate of 18-month rates. However as noted above, only 28% of PREVAIL subjects have actually reached 18 months of follow-up. Model based assumptions are therefore important to consider. The Panel will be asked to comment on the clinical significance of the second primary endpoint results with respect to ischemic stroke, and discuss the effectiveness of the device as an acceptable alternative to warfarin to prevent ischemic stroke.

<u>Examining the impact of using prior information from PROTECT AF</u>

Historical data from the PROTECT AF study was used as prior information with a discounting weight of 50% in the primary analyses of the first and second primary endpoints. To evaluate the impact of using <u>prior information from PROTECT AF</u>, the sponsor performed an analysis using only the PREVAIL data, and FDA performed an analysis using only the discounted PROTECT AF data that was used as prior information.

As shown in Table 12, when based only on the data from PREVAIL, the first primary endpoint 18-month rate ratio is 2.01, and the upper bound of the 95% credible interval for the rate ratio is 6.02. For comparison, when the discounted PROTECT AF data that was used as prior information in the PREVAIL Bayesian analysis was analyzed alone, the first primary endpoint 18-month rate ratio was 0.88, and the upper bound of the 95% credible interval was 1.79 (Table 13).

Table 12: First Primary Endpoint Using Only PREVAIL Study Data (Sponsor Analysis)

Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CI)	Rate Ratio Non-Inferiority Criteria	Non-Inferiority Criteria Met?
0.071	0.047	2.01 (0.56, 6.02)	95% CI Upper Bound <1.75	No

Table 13: First Primary Endpoint Results Using Only PROTECT AF Prior Distribution (FDA Analysis)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non- Inferiority Criteria	Non-inferiority Criteria Met?
0.062	0.077	0.88 (0.37, 1.79)	95% CrI Upper Bound < 1.75	No

Similar results were observed for the second primary endpoint. Based on the data only from PREVAIL, the second primary endpoint 18-month rate ratio is 40.3 and the upper bound of the 95% credible interval for the rate ratio is 83.6. The second primary endpoint 18-month rate difference is 0.0166 and the upper bound of the 95% credible interval is 0.0535 (Table 14). For comparison, when the discounted PROTECT AF data that was used as prior information in the PREVAIL Bayesian analysis was analyzed alone, the 18-month rate ratio was 1.4 (with a 95% credible interval upper bound of 4.3), and the 18-month rate difference was 0.0003 (with a 95% credible interval upper bound of 0.0317, Table 15).

Table 14: Second Primary Endpoint Using Only PREVAIL Study Data (Sponsor Analysis)

Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CI)	Rate Ratio Non-Inferiority Criteria	18 Month Rate Difference (95% CI)	Rate Difference Non-Inferiority Criteria	Non-inferiority Criteria Met?
0.0301	0.0135	40.3 (0.4, 83.6)	95% CI Upper Bound < 2.0	0.0166 (-0.0246, 0.0535)	95% CI Upper Bound < 0.0275	No

Table 15: Second Primary Endpoint Results Using Only PROTECT AF Prior Distribution (FDA Analysis)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criteria	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criteria	Non-inferiority Criteria Met?
0.0249	0.0246	1.4 (0.3, 4.3)	95% CrI Upper Bound < 2.0	0.0003 (-0.0342, 0.0317)	95% CrI Upper Bound < 0.0275	No

<u>FDA Comment</u>: Although the historical PROTECT AF was discounted 50% to avoid overly influencing the study outcomes, incorporating the PROTECT AF data in the Bayesian analyses has a noticeable effect on the first and second endpoint results, as evidenced by the differences in the point estimates of the event rates seen in PREVAIL vs. PROTECT AF. Note that the credible intervals are wide as a result of the smaller sample size when only PREVAIL data are considered.

<u>Constant hazard rate assessment</u>

The piecewise exponential model used for the first and second primary endpoint analyses assumed a constant hazard rate for each treatment group at particular follow-up intervals (i.e., constant primary endpoint event rate over a particular follow-up interval). Both the sponsor and FDA conducted an evaluation of the pre-specified assumption of constant hazard rates for this model based on PREVAIL data and concluded that the constant hazard rate assumption was reasonable (see Appendix C for more technical details).

6.6 *THIRD PRIMARY ENDPOINT RESULTS*

The primary analysis of the third primary endpoint was a comparison to a performance goal of the composite rate of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later. This endpoint was analyzed for the subjects randomized to the device group only via a pre-specified Bayesian method based on a conjugate beta-binomial model and prior information from the PROTECT AF and CAP historical data with no discounting (see Appendix C). There were 6 events in 6 subjects (Table 16) out of 269 total PREVAIL device group subjects and an event rate was 2.2%. The one-sided 95% credible interval upper bound based on the Bayesian analysis was 2.652%, which met the performance goal of 2.67% (Table 17). Therefore, success for the third primary safety endpoint was achieved.

Table 16: PREVAIL Third Primary Endpoint Events by Type (ITT)

Device Group		
Type	**N Events**	**% of Subjects**
Device Embolization	2	0.7%
AV Fistula	1	0.4%
Cardiac Perforation	1	0.4%
Pericardial Effusion with Cardiac Tamponade	1	0.4%
Major Bleed Requiring Transfusion	1	0.4%

Table 17: PREVAIL Third Primary Endpoint Results (ITT)

Device Group		
N Subjects	**% (n/N)**	**95% CrI (Bayesian analysis)**
269	2.2% (6/269)	2.652%

CrI is one-sided, N = number, CrI = credible interval

Two subjects who experienced third primary endpoint events also had additional adverse events captured in the primary endpoint:

- Subject [redacted] had a cardiac arrest (pulseless electrical activity) when the device became entangled in the mitral valve apparatus. The subject was resuscitated and underwent emergency CT surgery to remove the device. The subject suffered anoxic encephalopathy and an ischemic stroke (with the stroke event captured in the first primary endpoint).
- Subject [redacted] fell 5 days post-device implant and suffered a subdural hematoma that was also adjudicated as a hemorrhagic stroke. The subject was on ASA plus warfarin at the time of the event. The subject died 7 months later (adjudicated as a respiratory

death). The device embolization was captured in the third primary endpoint, and the hemorrhagic stroke was captured in the first primary endpoint.

FDA Comment: The Panel will be asked to comment on whether the new procedural safety data from PREVAIL address the acute procedural safety concerns raised in PROTECT AF.

6.7 ADDITIONAL ANALYSES

New Investigator/New Site Enrollment and Results

There were 50 operators in the study. Of these, 24/50 (48%) were new operators and 26/50 (52%) had prior WATCHMAN experience. New operators enrolled 39.1% of subjects (159/407), exceeding the protocol requirement of a minimum of 25% of enrolled subjects (Table 18). New sites contributed 38.8% (158/407) of randomized subjects, exceeding the protocol requirement of a minimum of 20% of enrolled subjects.

Table 18: PREVAIL New and Experienced Enrollment

Category	Device Group	Control Group	Randomized Total	Percentage Enrolled
New Site	104/269 (38.7%)	54/138 (39.1%)	158/407	38.8%
Experienced Site	165/269 (61.3%)	84/138 (60.9%)	249/407	61.2%
New Operator	105/269 (39.0%)	54/138 (39.1%)	159/407	39.1%
Experienced Operator	164/269 (61.0%)	84/138 (60.9%)	248/407	60.9%

Implant success for experienced operators was 95% (173/182) for all subjects and 96% (156/162) for randomized device subjects. Implant success for new operators was 95% (130/137) for all subjects and 93% (96/103) in randomized subjects. New operators successfully implanted 100% of the Roll-in subjects (their first implant attempts). Primary endpoint analyses stratified by operator experience are presented in Table 19.

Table 19: Primary Endpoint by Operator Type – Randomized Device Subjects Only

	New Operators		Experienced Operators	
	N Events/ N Subjects	% of Subjects	N Events/ N Subjects	% of Subjects
First Primary Endpoint (Composite efficacy)	2/105	1.9%	12/164	7.3%
Second Primary Endpoint (Late ischemic events)	0/105	0.0%	5/164	3.0%
Third Primary Endpoint (Acute safety)	2/105	1.9%	4/164	2.4%

FDA Comment: Enrollment of subjects by new operators and at new sites, to augment the evaluation of the procedural learning curve, exceeded target quotas. Note that device implantation by new operators was not associated with reduced rates of implant success or an increased risk of major adverse events, indicating that the training program implemented by the sponsor was effective.

Warfarin Compliance

The overall time in therapeutic range (TTR) for the control group was 68%, and compliance with INR monitoring (defined as an INR measurement taken at least every 28 days) was approximately 85%. The percentage of control group subjects who permanently discontinued warfarin therapy was 10.9% (15/138). Of these 15 subjects, 7 switched to a newer anticoagulant drug, 3 experienced warfarin related adverse events, 3 refused to continue warfarin therapy, and 2 underwent left atrial appendage removal.

The percentage of successfully implanted device group subjects able to discontinue warfarin therapy 45 days post-procedure was 92% (227/246). Of the 19 subjects that did not discontinue warfarin therapy at 45 days, only 5 continued on warfarin therapy due to jet size of ≥5 mm; the remaining continued on warfarin therapy for other reasons not related to the device seal. Reasons for continuing warfarin therapy after 45 days included: thrombus on the device found on TEE (3 subjects), cardioversion performed at 45 days requiring continued warfarin use (2 subjects), delay in review of TEE results by physician adjusting the drug regimen (2 subjects), 45-day TEE not performed (2 subjects), physician requested repeat TEE (1 subject), delay in filling clopidogrel prescription (1 subject), and physician choice to continue warfarin therapy until a complete seal around the device was demonstrated (1 subject). At 6 months post-WATCHMAN implant, the percentage of subjects who discontinued warfarin increased to 98%.

FDA Comment: Compliance with INR monitoring, rates of achieving a therapeutic INR, and rates of warfarin discontinuation (among device subjects) were reasonably high in PREVAIL.

Post-Procedure Analysis

This analysis included all randomized control subjects and all randomized WATCHMAN subjects who underwent an implant attempt (defined as venous access). For the device group, the start time of follow-up was the day following the implant attempt (all events occurring prior to this day were excluded), whereas for the control group, the start time of follow-up was the day of randomization. Censoring was otherwise performed as in the primary ITT analysis, and the primary Bayesian model was applied to this analysis population for the first two primary endpoints.

For the first primary endpoint (18-month rate of stroke, cardiovascular or unexplained death, and systemic embolism) post-procedure analysis (Table 20), the 18-month rate was 0.058 for the device group and 0.063 for the control group. The 18-month rate ratio was 0.98 with a 95% credible interval of 0.51 to 1.747, which met the non-inferiority criterion of 1.75.

Table 20: First Primary Endpoint Results (Post-Procedure)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criteria
0.058	0.063	0.98 (0.51, 1.747)	95% CrI Upper Bound < 1.75

CrI = credible interval

For the second primary endpoint (18-month rate of stroke and systemic embolism, excluding events occurring in the first 7 days), the 18-month rate was 0.0255 for the device group and 0.0199 for the control group (Table 21). The 18-month rate ratio was 1.6 (with a 95% credible interval of 0.5 to 4.3), and the 18-month rate difference was 0.0056 (with a 95% credible interval of -0.0187 to 0.0277. The upper bounds of the 95% credible intervals for both the rate ratio and the rate difference (4.3 and 0.0277, respectively) were both higher than their respective non-inferiority criteria of 2.0 and 0.0275; statistical non-inferiority for the second primary endpoint was not met.

Table 21: Second Primary Endpoint Results (Post-Procedure)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CI)	Rate Ratio Non-Inferiority Criteria	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criteria
0.0255	0.0199	1.6 (0.5, 4.3)	95% CI Upper Bound < 2.0	0.0056 (-0.0187, 0.0277)	95% CrI Upper Bound < 0.0275

<u>Per Protocol Analysis #1</u>

This analysis included all randomized control subjects who began warfarin therapy and all randomized WATCHMAN subjects who were successfully implanted and discontinued warfarin therapy following device implantation. This analysis allowed for examination of the effects of treatment after successful implant and after warfarin therapy ended.

For the device group, the start time of follow-up was the day following the discontinuation of warfarin following device implantation (all events occurring prior to this day were excluded). For the control group, the start time of follow-up was the day of randomization. Device subjects without an implanted device, those who did not discontinue warfarin therapy following implant, or those with events occurring prior to the date of warfarin discontinuation following implant were excluded from the analysis. Censoring was otherwise performed as in the primary ITT analysis, and the primary Bayesian model was applied to this analysis population for the first two primary endpoints.

For per-protocol analysis #1 for the first primary endpoint (18-month rate of stroke, cardiovascular or unexplained death, and systemic embolism), the event rate was 0.048 for the device group and 0.061 for the control group (Table 22). The 18-month rate ratio was 0.84 with a 95% credible interval of 0.41 to 1.55. The 95% CrI upper bound of 1.55 was lower than the non-inferiority criterion of 1.75.

Table 22: First Primary Endpoint Results (Per-Protocol #1)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.048	0.061	0.84 (0.41, 1.55)	95% CrI Upper Bound < 1.75

CrI = credible interval

For the second primary endpoint (18-month rate of stroke and systemic embolism, excluding events occurring in the first 7 days), the event rate was 0.0259 for the device group and 0.0201 for the control group (Table 23). The 18-month rate ratio was 1.6 with a 95% credible interval of 0.5 to 4.3, and an 18-month rate difference of 0.0058 with a 95% credible interval of -0.0191 to 0.0285. The upper bounds of the 95% credible intervals for both the rate ratio and the rate difference (4.3 and 0.0285, respectively) were higher than their respective non-inferiority criteria of 2.0 and 0.0275.

Table 23: Second Primary Endpoint Results (Per-Protocol #1)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0259	0.0201	1.6 (0.5, 4.3)	95% CI Upper Bound < 2.0	0.0058 (-0.0191, 0.0285)	95% CrI Upper Bound < 0.0275

Compared to the ITT analyses, there were 4 fewer events in the device group in Per-Protocol Analysis #1; that is, 4 primary endpoint events occurred while device group subjects were on warfarin.

<u>FDA Comment</u>: The exclusion of the time period before discontinuation of warfarin in the device group creates a substantial difference in follow-up between the device and control groups, which introduces potential bias by excluding some events that occurred in the device group but not the control group. As a result it is difficult to interpret any causal relationships between treatment groups and endpoint events.

<u>Per Protocol Analysis #2:</u>
This analysis included all randomized control subjects who began warfarin therapy and all randomized WATCHMAN subjects who were successfully implanted and discontinued clopidogrel therapy following device implantation. This analysis allowed for examination of the effects of treatment after successful WATCHMAN implantation when device subjects are on their final regimen of long-term aspirin only.

For the device group, the start time of follow-up was the day following the discontinuation of clopidogrel following device implantation (all events occurring prior to this day were excluded). For the control group, the start time of follow-up was the day of randomization. Device subjects without an implanted device, those who did not discontinue clopidogrel therapy, or those with endpoint events which occurred prior to the date of clopidogrel discontinuation were excluded from the analysis. Censoring was otherwise performed as in the primary ITT analysis, and the primary Bayesian model was applied to this analysis population for the first two primary endpoints.

For per-protocol analysis #2 for the first primary endpoint (18-month rate of stroke, cardiovascular or unexplained death, and systemic embolism), the event rate was 0.058 for the device group and 0.062 for the control group (Table 24). The 18-month rate ratio was 1.00 with a 95% credible interval of 0.47 to 1.88. The 95% CrI upper bound of 1.88 was higher than the non-inferiority criterion of 1.75.

Table 24: First Primary Endpoint Results (Per-Protocol #2)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.058	0.062	1.00 (0.47, 1.88)	95% CrI Upper Bound < 1.75

CrI = credible interval

For the second primary endpoint (18-month rate of stroke and systemic embolism, excluding events occurring in the first 7 days), the 18-month rate was 0.0235 for the device group and 0.0201 for the control group (Table 25). The 18-month rate ratio was 1.5 with a 95% credible interval of 0.4 to 4.1, and the 18-month rate difference was 0.0035 with a 95% credible interval of -0.0221 to 0.0293. The upper bounds of the 95% credible intervals for both the rate ratio and the rate difference (4.1 and 0.0293, respectively) were higher than their respective non-inferiority criteria of 2.0 and 0.0275.

Table 25: Second Primary Endpoint Results (Per-Protocol #2)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0235	0.0201	1.5 (0.4, 4.1)	95% CrI Upper Bound < 2.0	0.0035 (-0.0221, 0.0293)	95% CrI Upper Bound < 0.0275

Compared to the ITT analyses, there were 9 fewer events in the device group in Per-Protocol Analysis #2; that is, 9 primary endpoint events occurred before device group subjects discontinued clopidogrel.

FDA Comment: Similar to Per-Protocol Analysis #1, the exclusion of the time period before discontinuation of warfarin in the device group creates a substantial difference in follow-up between the device and control groups, which introduces potential bias by excluding some events that occurred in the device group but not the control group. As a result it is difficult to interpret any causal relationships between treatment groups and endpoint events.

All-Cause Mortality: PREVAIL Data Only

There were 13 deaths in the device group and 5 deaths in the control group. The sponsor analyzed the mortality data using the same Bayesian model as was used for the first and second primary endpoints (Table 26). The 18-month rate in the device group was 0.028 compared to 0.045 in the control group. The 18-month rate ratio was 0.67, and the 95% credible interval for the rate ratio was 0.27 to 1.41. The sponsor concluded that none of the deaths in the device group were due to the device or implant procedure.

Table 26: All-Cause Mortality Results

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)
0.028	0.045	0.67 (0.27, 1.41)

The Kaplan-Meier curve and estimates for the all-cause mortality analysis are included in Figure 5 and Table 27, respectively.

Figure 5: Kaplan-Meier Curve: Freedom from All-Cause Mortality

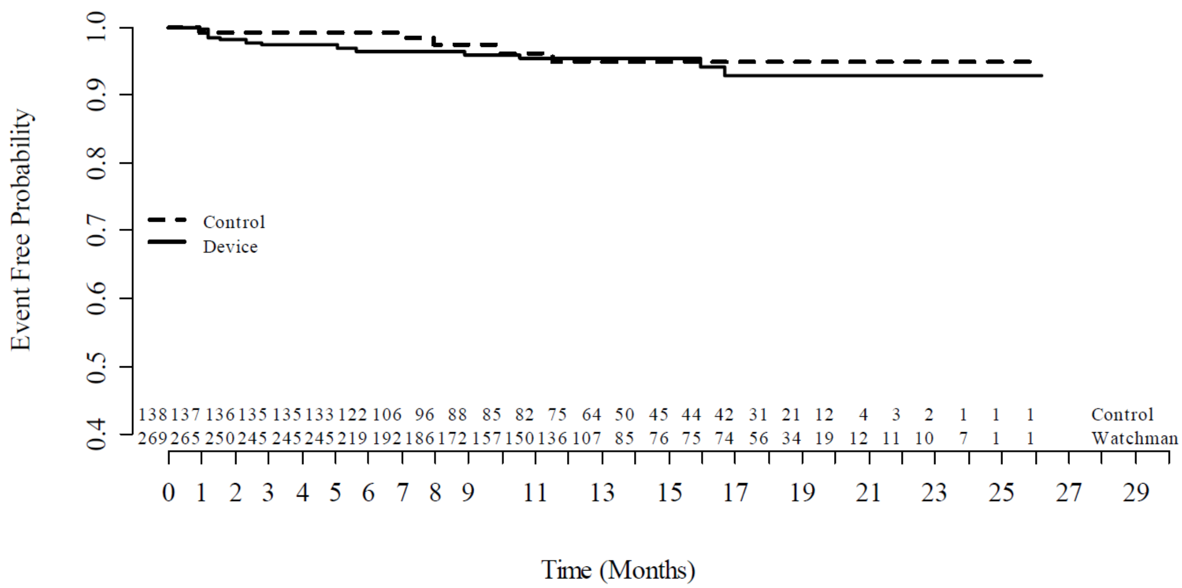


Table 27: Kaplan-Meier Estimates: Freedom from All-Cause Mortality

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	4	4	98.5 (96.0, 99.4)	1	1	99.3 (95.0, 99.9)
6-months	5	9	96.5 (93.4, 98.2)	0	1	99.3 (95.0, 99.9)
1-year	2	11	95.3 (91.6, 97.4)	4	5	95.0 (88.2, 97.9)
2-year	2	13	92.8 (87.0, 96.1)	0	5	95.0 (88.2, 97.9)

Randomization Allocation (2 Device: 1 Control)

FDA Comment: Review of the clinical narratives indicates no direct causality between either the WATCHMAN device or implant procedure and mortality.

Other Serious Adverse Events: PREVAIL Data Only

There were a number of procedure-related serious adverse events (SAEs) among device subjects (Table 28) that were not captured in the primary endpoints, including major bleeding events, which are discussed below. Events categorized as 'other study related' events in Table 30 consisted of prolonged urinary retention, prolonged post-procedure nausea, post-procedure congestive heart failure (CHF), contrast-related nephropathy and anoxic encephalopathy. The sponsor also reported non-device- or procedure-related SAEs in Table 29, including primary endpoint events, in both the device and control groups.

Table 28: Summary of Device- or Procedure-Related Events – SAEs (Device Subjects Only)

Event Type	Total Events	Subjects with Events	Device Related	Procedure Related
Other Study Related	5	4	1	5
Pericardial Effusion with Cardiac Tamponade	4	4	4	4
Infection	3	3	0	3
Device Embolization	2	2	2	2
Gastrointestinal Bleeding	2	2	0	2
Hematoma	2	2	0	2
Major Bleed Requiring Transfusion	2	2	0	2
Respiratory Failure	2	2	0	2
AV Fistula	1	1	0	1
Anemia Requiring Transfusion	1	1	0	1
Cardiac Perforation	1	1	1	1
Respiratory Insufficiency	1	1	0	1
Stroke – Ischemic	1	1	1	1
Systemic Embolism	1	1	1	0
Totals:	*28*	*23*	*10*	*27*

Randomization Allocation (2 Device: 1 Control)

Table 29: Summary of SAEs – Not Related to the Device or Implant Procedure

	Device	Control

Event Type	Events	Subjects with Events	Events	Subjects with Events
Death	13	13	5	5
Gastrointestinal Bleeding	10	10	3	3
Stroke - Ischemic	4	4	1	1
Transient Ischemic Attack (TIA)	3	3	1	1
Epistaxis	2	1	2	2
Other Study Related	2	2	1	1
Subdural Hematoma	2	2	0	0
Cranial Bleed	1	1	0	0
Major Bleed Requiring Transfusion	1	1	0	0
Pseudoaneurysm	1	1	0	0
Stroke - Hemorrhagic	1	1	0	0
Bleeding, Other (retroperitoneal and abdominal muscle hematomas)	0	0	1	1
Hematuria	0	0	1	1
Totals:	*40*	*34*	*15*	*13*

Randomization Allocation (2 Device: 1 Control)

Major Bleeding: PREVAIL Data Only

Major bleeding was defined as events adjudicated as SAEs[12] that were clinically grouped as bleeding events. Within 45 days (while the device group subjects were still on warfarin therapy), there were 18 events in the device group and 0 events in the control group. After 45 days, there were 6 events in the device group and 7 events in the control group (Table 30).

Table 30: PREVAIL Event Free Rates of Major Bleeding

	Device Group			Control Group		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	14	14	94.8 (91.3, 96.9)	0	0	100.0 (100.0, 100.0)
45-days	4	18	93.3 (89.5, 95.7)	0	0	100.0 (100.0, 100.0)
6-months	6	24	90.8 (86.5, 93.7)	3	3	97.7 (93.0, 99.3)
1-year	0	24	90.8 (86.5, 93.7)	4	7	93.4 (86.5, 96.9)
2-year	0	24	90.8 (86.5, 93.7)	0	7	N/A

Randomization Allocation (2 Device: 1 Control)

The types of bleeding events in the device vs. control groups are summarized in Table 31. Of the 24 total bleeding events in the device group, there were 8 subjects with gastrointestinal (GI)

[12] As defined the PREVAIL protocol, an adverse event is considered serious if it results in one of the following:

- Death
- Life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Permanent impairment of a body function or permanent damage to a body structure

bleeding, 4 pericardial effusions, 4 hematomas (2 of which were subdural hematomas), 3 major bleeds requiring transfusion, and one subject each with hemorrhagic stroke, arteriovenous (AV) fistula, cardiac perforation, and epistaxis. Of the 7 total bleeding events in the control group, there were 3 subjects with GI bleeding, 2 subjects with epistaxis, one subject with hematuria, and one with retroperitoneal and abdominal muscle hematomas.

Table 31: Type and Timing of Major Bleeding Events in PREVAIL

	Device Events (Subjects)					Control Events (Subjects)				
Event	**All Events Through 2 Years**	**0-7 days**	**8-45 days**	**45 days-6 months**	**6 months-1 year**	**All Events Through 2 Years**	**0-7 days**	**8-45 days**	**45 days-6 months**	**6 months-1 year**
AV Fistula	1	1	0	0	0	0	0	0	0	0
Bleeding, Other	0	0	0	0	0	1	0	0	0	1
Cardiac Perforation	1	1	0	0	0	0	0	0	0	0
Cranial Bleed	1	1	0	0	0	0	0	0	0	0
Epistaxis	1	0	0	1	0	2	0	0	1	1
Gastrointestinal Bleeding	8	2	2	4	0	3	0	0	2	1
Hematoma	2	1	1	0	0	0	0	0	0	0
Hematuria	0	0	0	0	0	1	0	0	0	1
Major Bleed Requiring Transfusion	3	3	0	0	0	0	0	0	0	0
Pericardial Effusion with Cardiac Tamponade	4	4	0	0	0	0	0	0	0	0
Stroke - Hemorrhagic	1	1	0	0	0	0	0	0	0	0
Subdural Hematoma	2	0	1	1	0	0	0	0	0	0
Total	**24**	**14**	**4**	**6**	**0**	**7**	**0**	**0**	**3**	**4**

Randomization Allocation (2 Device: 1 Control)

<u>FDA Comment</u>: PREVAIL was not designed to compare major bleeding rates between subjects treated with the WATCHMAN device or warfarin, and bleeding was not analyzed by scales used in other major clinical trials (e.g., GUSTO, TIMI). A postulated benefit of the WATCHMAN device compared with anticoagulation therapy is a reduced rate of bleeding events; however, there did not appear to be a signal of a reduction in total bleeding events or a reduction in bleeding events over time in the WATCHMAN device group compared to the control group. The Panel will be asked to comment on the clinical significance of the major bleeding events.

<u>Device Thrombus: PREVAIL Data Only</u>

There were 13 cases of WATCHMAN device thrombus. Although these events would be considered important clinically, none of these events met the criteria for serious adverse events.

Device recapture and malfunctions

The sponsor reported a 95.1% (252/265) implant procedure success rate. Not counted in these data are the number of device recaptures. If release criteria were not met, the device was recaptured, removed, and replaced, and another attempt was made to implant the device. Approximately 70% (184/265) of devices were adequately placed on the first attempt, and 30% required one or more recaptures with approximately 2% (5/265) of devices recaptured four or more times.

Device malfunctions were reported in 11 out of 265 implant attempts when there was a problem with the packaging, breakage or failure of the device to perform as intended. The majority (7/11) of these malfunctions were problems with the access system being kinked, bent, or damaged.

FDA Comment: There was a lower percentage of device recaptures in PREVAIL versus PROTECT AF, in which 42% of implant procedures required one or more recaptures.

Subgroup Analyses

The sponsor provided analyses of effects of baseline covariates (gender, age, $CHADS_2$ category, AF pattern, LVEF, and device size) on the primary endpoints (Tables 32 and 33, respectively). Subjects with $CHADS_2$ scores of 4-6 experienced a significantly greater number of first and second primary endpoint events than subjects with $CHADS_2$ scores of 1-3.

Table 32: First Primary Endpoint by Baseline Covariate

Covariate	Hazard Ratio (95% CI)	P-Value
Gender (Female vs. Male)	0.48 (0.14, 1.65)	0.2445
Age (Above vs. Below Median)	1.83 (0.71, 4.71)	0.2135
$CHADS_2$ Score (1-3 vs. 4-6)	0.28 (0.11, 0.72)	0.0079
AF Pattern (Non-Paroxysmal vs. Paroxysmal)	1.99 (0.74, 5.29)	0.1703
LVEF (Above vs. Below Median)	0.50 (0.19, 1.34)	0.1687
Device Size (21, 24mm vs. 27, 30, and 33mm)	0.99 (0.35, 2.82)	0.9820

Table 33: Second Primary Endpoint by Baseline Covariate

Covariate	Hazard Ratio (95% CI)	P-Value
Gender (Female vs. Male)	1.18 (0.22, 6.45)	0.8470
Age (Above vs. Below Median)	5.80 (0.68, 49.66)	0.1086
$CHADS_2$ Score (1-3 vs. 4-6)	0.11 (0.02, 0.61)	0.0117
AF Pattern (Non-Paroxysmal vs. Paroxysmal)	4.98 (0.58, 42.65)	0.1426
LVEF (Above vs. Below Median)	0.50 (0.09, 2.75)	0.4287
Device Size (27, 30, and 33mm vs. 21, 24mm)	0.26 (0.03, 2.36)	0.2329

Subgroup analyses of the first (Table 34) and second (Table 35) primary endpoints stratified by treatment group showed no statistically significant differences between the WATCHMAN and Control groups. Similarly, there were no statistically significant differences among baseline covariates for the third primary endpoint (Table 36, WATCHMAN device only).

FDA Comment: The small number of subjects in each subgroup may preclude the detection of outcome differences in these analyses.

Table 34: First Primary Endpoint by Baseline Covariate and Randomization

Subgroup	Device % (n/N)	Control % (n/N)	Subgroup Hazard Ratio (95% CI)	Subgroup P-value	Interaction P-value
Gender					
Female	2.3% (2/87)	2.9% (1/35)	1.05 (0.09, 11.65)	0.967	0.490
Male	6.6% (12/182)	2.9% (3/103)	0.43 (0.12, 1.51)	0.187	
Age					
Above Median	7.2% (9/125)	3.1% (2/64)	0.38 (0.08, 1.76)	0.217	0.558
Below Median	3.5% (5/144)	2.7% (2/74)	0.75 (0.15, 3.87)	0.732	
$CHADS_2$ Category					
1-3	4.5% (10/223)	0.0% (0/110)	0.00	0.993	0.988
4-6	8.7% (4/46)	14.3% (4/28)	1.48 (0.37, 5.93)	0.584	
AF Pattern					
Other	6.5% (9/138)	4.5% (3/67)	0.63 (0.17, 2.31)	0.483	0.649
Paroxysmal	3.8% (5/131)	1.4% (1/71)	0.36 (0.04, 3.05)	0.346	
LVEF					
Above Median	2.3% (3/129)	4.2% (3/72)	1.70 (0.34, 8.40)	0.518	0.091
Below Median	7.9% (11/139)	1.5% (1/65)	0.18 (0.02, 1.39)	0.100	
Device Size (Device Group Only)					
21 mm	7.7% (3/39)	.	.	.	.
24 mm	4.8% (4/83)	.	.	.	.
27 mm	4.8% (4/83)	.	.	.	.
30 mm	5.4% (2/37)	.	.	.	.
33 mm	10.0% (1/10)	.	.	.	.

Table 35: Second Primary Endpoint by Baseline Covariate and Randomization

Subgroup	Device % (n/N)	Control (n/N)	Subgroup Hazard Ratio (95% CI)	Subgroup P-value	Interaction P-value
Gender					
Female	1.1% (1/87)	2.9% (1/35)	1.96 (0.12, 31.53)	0.633	0.995
Male	2.2% (4/182)	0.0% (0/103)	N/A	0.995	
Age					
Above Median	3.2% (4/125)	1.6% (1/64)	0.41 (0.05, 3.67)	0.425	0.995
Below Median	0.7% (1/144)	0.0% (0/74)	N/A	0.998	
CHADS Category					
1-3	0.9% (2/223)	0.0% (0/110)	N/A	0.997	0.995
4-6	6.5% (3/46)	3.6% (1/28)	0.45 (0.05, 4.35)	0.489	
AF Pattern					
Other	2.9% (4/138)	1.5% (1/67)	0.46 (0.05, 4.16)	0.493	0.995
Paroxysmal	0.8% (1/131)	0.0% (0/71)	N/A	0.998	
LVEF					
Above Median	0.8% (1/129)	1.4% (1/72)	1.68 (0.10, 26.83)	0.715	0.994
Below Median	2.9% (4/139)	0.0% (0/65)	N/A	0.995	
Device Size					
21 mm	5.1% (2/39)	N/A	N/A		
24 mm	2.4% (2/83)				
27 mm	1.2% (1/83)				
30 mm	0.0% (0/37)				
33 mm	0.0% (0/10)				

Table 36: Third Primary Endpoint by Baseline Covariate

Subgroup	Device % (n/N)	Hazard Ratio (95% CI)	P-Value
Gender			
Female	3.4% (3/87)	2.12 (0.43, 10.49)	0.358
Male	1.6% (3/182)		
Age			
Above Median	2.4% (3/125)	1.15 (0.23, 5.70)	0.864
Below Median	2.1% (3/144)		
$CHADS_2$ Score			
CHADS 1-3	2.7% (6/223)	444E4	0.994
CHADS 4-6	0.0% (0/46)		
AF Pattern			
Other	2.9% (4/138)	1.90 (0.35, 10.37)	0.459
Paroxysmal	1.5% (2/131)		
LVEF			
Above Median	1.6% (2/129)	0.53 (0.10, 2.90)	0.464
Below Median	2.9% (4/139)		
Device Size			
21 mm	0.0% (0/39)	0.00 (0.00,)	0.997
24 mm	0.0% (0/83)	0.00 (0.00,)	0.996
27 mm	3.6% (3/83)	0.34 (0.04, 3.24)	0.347
30 mm	2.7% (1/37)	0.25 (0.02, 3.97)	0.325
33 mm	10.0% (1/10)	.	.

7 ADDITIONAL DATA

7.1 LONG-TERM PROTECT AF FOLLOW-UP DATA

See Appendix A for a summary of the original design of PROTECT AF and previously submitted primary endpoint results. The sponsor provided an analysis of a 1588 patient-year dataset, which represents the final pre-specified analysis, and a 2621 patient-year dataset that consists of the most recent follow-up available on all subjects.

FDA Comment: Although there are limitations to the robustness of the PROTECT AF data, the long-term clinical outcomes from PROTECT AF should be considered as part of the totality of the information available on the safety and effectiveness of the WATCHMAN device, particularly since the length of follow-up in PROTECT AF (average follow-up of 45.7 months) is far greater than in PREVAIL (average follow-up of 11.8 months).

Follow-up and Subject Withdrawal
Compliance with follow-up visits was approximately 95%. The overall mean follow-up time was 45.7 ± 20.4 months for randomized subjects, and 41.6% (294/707) of subjects have completed the 5 years of follow-up as required in the protocol.

Among all subjects who exited the trial, 32.4% (150/463) of subjects in the device group and 45.1% (110/244) of control subjects exited the study early for any reason (denoted as "All Early Exits" in Table 37).

Table 37: PROTECT AF Subject Withdrawal and Lost to Follow-Up

Pt-Yr Analysis	Device		Control	
	All Early Exits N/463 (% of Subjects)	Withdrawal/LTF Exits N/463 (% of Subjects)	All Early Exits N/244 (% of Subjects)	Withdrawal/LTF Exits N/244 (% of Subjects)
600 pt-yr	76 (16.4)	7 (1.5)	35 (14.3)	18 (7.4)
1588 pt-yr	111 (24.0)	15 (3.2)	76 (31.2)	38 (15.6)
2621 pt-yr	150 (32.4)	30 (6.5)	110 (45.1)	56 (23.0)

LTF: Lost to follow-up

Early exits included subjects who died, device subjects with no implant or no implant attempted, subjects who voluntarily withdrew or were lost to followup, and other reasons (Table 38). In the device group, these other reasons included: nine subjects who did not have the device implanted due to embolization, explant, or aborted procedure; two subjects who had medical status that made follow-up unmanageable; and one subject who exited prior to implant due to a finding of amyloidosis.

In the control group, other reasons included: six subjects who permanently discontinued warfarin therapy; three subjects with medical conditions that did not allow for continued follow-up; and one subject who relocated overseas.

Table 38: PROTECT AF Subject End of Study Summary

Discontinuation Reason	Device N/463 (%)	Control N/244 (%)	Total N/707 (%)
Subject Successfully Completed Study	202 (43.6%)	92 (37.7%)	294 (41.6%)
Death	57 (12.3%)	44 (18.0%)	101 (14.3%)
No Device Implanted (Exited by 45-Day Visit)	41 (8.9%)	NA	41 (5.8%)
Subject Consent Withdrawn	17 (3.7%)	45 (18.4%)	62 (8.8%)
Lost to Follow-up	13 (2.8%)	11 (4.5%)	24 (3.4%)
Other	12 (2.6%)	10 (4.1%)	22 (3.1%)
Outside Implant Window (No Implant Attempt)	10 (2.2%)	NA	10 (1.4%)
Subjects Still in Follow-Up	111 (24.0%)	42 (17.2%)	153 (21.6%)
Total	*463*	*244*	*707*

Subjects who voluntarily withdrew from the study early (withdrew consent) or were lost to follow-up include 6.5% (30/463) of device subjects and 23.0% (56/244) of control subjects (Table 37). Since the 600 patient-year (pt-yr) analysis submitted in the previous PMA (included in Table 37 for comparison), the number of early study exits for the control group has increased by 8.2% between the 600 and 1588 pt-yr analyses and 7.4% between the 1588 and 2621 pt-yr analyses.

<u>FDA Comment</u>: The rate of withdrawal of consent was nearly 5-fold greater in the control group (18.4%) vs. the device group (3.7%) as shown in Table 38. The rate of voluntary withdrawals plus lost to follow-up was 3.5-fold greater in the control group (23%) vs. the device group (6.5%). The rate of subject withdrawal, particularly the disparity in withdrawal rates between treatment groups, could lead to bias against the control group and favoring of the device group for the long-term event rate comparisons presented below, considering that the hazard rates decrease over time.

<u>Primary Effectiveness Endpoint</u>

For both the 1588 and 2621 patient-year data analyses, the 95% credible interval for the relative risk (rate ratio) is lower than the non-inferiority margin of 2.0, and the posterior probability of non-inferiority for each dataset exceeds the pre-specified non-inferiority criterion of 0.975 (Table 39). For the 2621 patient-year dataset, the posterior probability that the event rate for the device group is less than the event rate for the control group (superiority) was 0.96, exceeding the superiority criterion of 0.95.

Table 39: PROTECT AF Primary Effectiveness Endpoint Results (ITT)

Analysis Cohort	Device		Control		Relative Risk (95% CrI)		Posterior Probabilities	
	Rate (95% CrI)		Rate (95% CrI)				Non-inferiority	Superiority
1588 pt-yrs	3.0	(2.1,4.3)	4.3	(2.6, 5.9)	0.71	(0.44, 1.30)	>0.999	0.846
2621 pt-yrs	2.3	(1.7, 3.2)	3.8	(2.5, 4.9)	0.60	(0.41, 1.05)	>0.999	0.960

Pt-yrs = patient-years CrI = credible interval
Rate = event rate per 100 patient-years (calculated as 100*N events/Total patient-years) Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate

<u>FDA Comment</u>: A Bayesian approach based on a Poisson-Gamma model was used to evaluate the primary effectiveness endpoint, in particular the posterior probabilities in Table 39. Specifically, the number of events was assumed to follow a Poisson distribution with parameter λ (hazard rate) assumed to be constant across the entire follow-up period within each treatment group. As discussed at the previous Panel meeting, this assumption is not valid. Therefore, the model used to estimate the event rates is not accurate and sole reliance on the statistical results from the primary analysis may be problematic.

The Kaplan-Meier curve and estimates for the Primary Effectiveness ITT analysis are shown in Figure 6 and Table 40, respectively.

Figure 6: Kaplan-Meier Curve: Freedom from Primary Effectiveness Event 2621 pt-yrs (ITT)

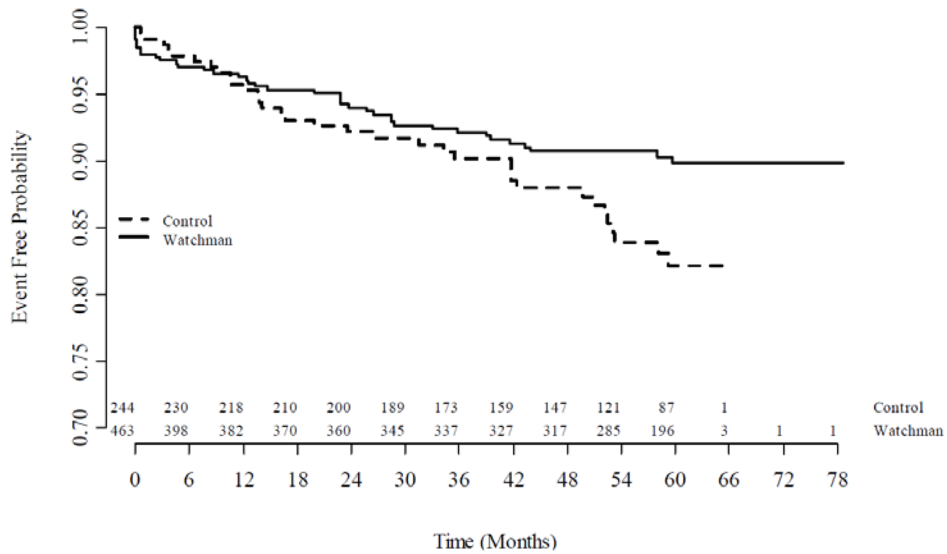


Table 40: Kaplan-Meier Estimates: Freedom from Primary Effectiveness Event 2621 Pt-Yrs (ITT)

	Device			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	7	7	98.5 (96.8, 99.3)	0	0	100.0 (100.0, 100.0)
45-days	2	9	98.0 (96.3, 99.0)	2	2	99.2 (96.7, 99.8)
6-months	4	13	97.1 (95.0, 98.3)	3	5	97.9 (95.1, 99.1)
1-year	3	16	96.3 (94.1, 97.7)	5	10	95.7 (92.2, 97.7)
2-year	9	25	94.0 (91.3, 95.9)	8	18	92.2 (87.9, 95.0)
3-year	7	32	92.1 (89.1, 94.4)	4	22	90.2 (85.4, 93.4)
4-year	5	37	90.8 (87.5, 93.2)	4	26	88.0 (82.8, 91.7)
5-year	2	39	89.9 (86.3, 92.5)	8	34	82.2 (75.6, 87.1)

Randomization Allocation (2 Device: 1 Control)

A comparative analysis of the primary effectiveness endpoint using a Cox proportional hazards model demonstrated similar results. The effectiveness event rate was 2.3/100 patient-years in the device group and 3.8/100 patient-years in the control group, corresponding to a hazard ratio of 0.61 with a 95% confidence interval of 0.38 to 0.97 (p=0.0348 for superiority).

The rates of the individual components of the primary effectiveness endpoint are shown in Table 41. The rate of ischemic stroke plus systemic embolism was numerically higher in the device group.

Table 41: Events Contributing to Primary Effectiveness Endpoint 2621 Pt-Yrs (ITT)

	Device		Control	
Type	**N Events**	**% of 463 Randomized Subjects**	**N Events**	**% of 244 Randomized Subjects**
Stroke - Ischemic	24	5.2%	10	4.1%
Death – Cardiovascular and Unexplained	11	2.4%	14	5.7%
Stroke - Hemorrhagic	2	0.4%	10	4.1%
Systemic Embolization	2	0.4%	0	0.0%

Randomization Allocation (2 Device: 1 Control)

In the device group, if one excludes the ischemic strokes in one subject whose event occurred after randomization but before a device implant was attempted and 5 subjects with peri-procedural strokes, the device group post-procedure ischemic stroke rate was 3.9%.

FDA Comment: The rates of hemorrhagic stroke and CV or unexplained death numerically favored the device group, and the ischemic stroke rate numerically favored the control group. Note that the absolute number of events is not directly comparable given the 2:1 Device:Control randomization ratio. The Panel will be asked to comment on the clinical significance of the primary effectiveness endpoint results in terms of the long-term safety and effectiveness of the WATCHMAN device.

Ischemic Stroke

To specifically evaluate the effectiveness of the device at preventing ischemic strokes, the sponsor analyzed the rate of ischemic strokes in the ITT population and the Post-Procedure population. The Post-Procedure population included only device subjects with an implant attempt. For device group subjects, the start time of follow-up was the day following the implant attempt (all events occurring prior to this day were excluded), whereas for the control group subjects the start time of follow-up was the day of randomization. Using the 2621 pt-yr dataset, the stroke rate in the device group was 1.4% in the ITT analysis and 1.1% in the Post-Procedure analysis (Table 42). In comparison, the stroke rate in the control group was 1.1% for both the ITT and Post-Procedure analyses. There were 6 peri-procedural ischemic strokes which contribute to the ITT analysis, but not the Post-Procedure analysis.

Table 42: Ischemic Stroke Rates by Patient-Year Dataset

Data Set	Device			Control			Relative Risk (95% CrI)
	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	
1588 pt-yrs (ITT)	463	19/1026.3	1.9 (1.1, 2.9)	244	8/564.9	1.4 (0.6, 2.4)	1.31 (0.66, 3.60)
1588 pt-yrs (Post-procedure)	449	13/1016.3	1.3 (0.7, 2.1)	244	8/564.9	1.4 (0.6, 2.4)	0.90 (0.42, 2.61)
2621 pt-yrs (ITT)	463	24/1720.7	1.4 (0.9, 2.1)	244	10/904.2	1.1 (0.5, 1.7)	1.26 (0.72, 3.29)
2621 pt-yrs (Post-procedure)	449	18/1710.6	1.1 (0.7, 1.7)	244	10/904.2	1.1 (0.5, 1.7)	0.95 (0.52, 2.58)

The Kaplan-Meier curve and estimates for the ITT analysis are shown in Figure 7 and Table 43, respectively. The-Kaplan Meier curve and estimates for the Post-Procedure analysis are shown in Figure 8 and Table 44, respectively.

Figure 7: Kaplan-Meier Curve: Freedom from Ischemic Stroke 2621 pt-yrs (ITT)

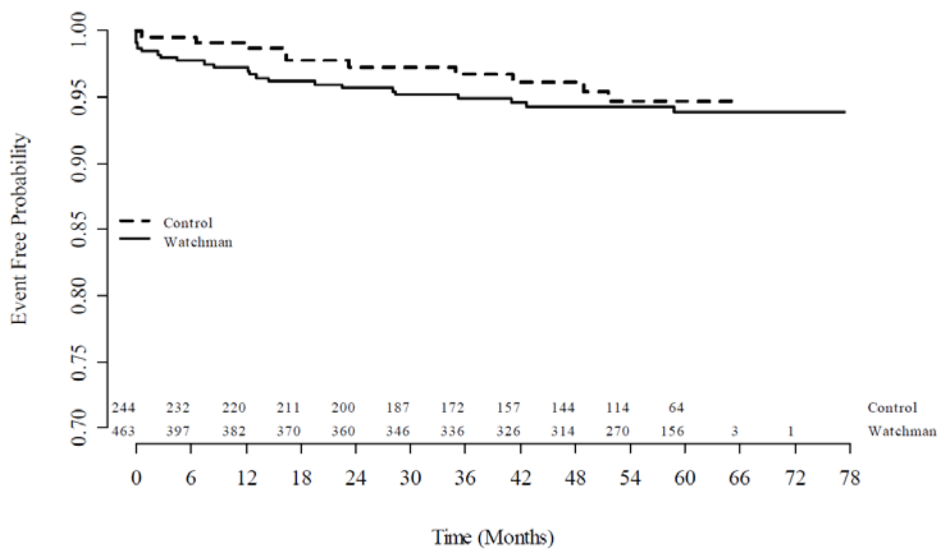


Table 43: Kaplan-Meier Estimates: Freedom from Ischemic Stroke 2621 pt-yrs (ITT)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	6	6	98.7 (97.1, 99.4)	0	0	100.0 (100.0, 100.0)
45-days	1	7	98.5 (96.8, 99.3)	1	1	99.6 (97.1, 99.9)
6-months	3	10	97.8 (95.9, 98.8)	0	1	99.6 (97.1, 99.9)
1-year	2	12	97.3 (95.2, 98.4)	1	2	99.2 (96.7, 99.8)
2-year	6	18	95.7 (93.3, 97.3)	4	6	97.3 (94.1, 98.8)
3-year	3	21	94.9 (92.3, 96.6)	1	7	96.7 (93.3, 98.4)
4-year	2	23	94.3 (91.5, 96.2)	1	8	96.1 (92.4, 98.1)
5-year	1	24	93.8 (90.9, 95.9)	2	10	94.7 (90.2, 97.2)

Randomization Allocation (2 Device: 1 Control)

Figure 8: Kaplan-Meier Curve: Freedom from Ischemic Stroke 2621 pt-yrs (Post-Procedure)

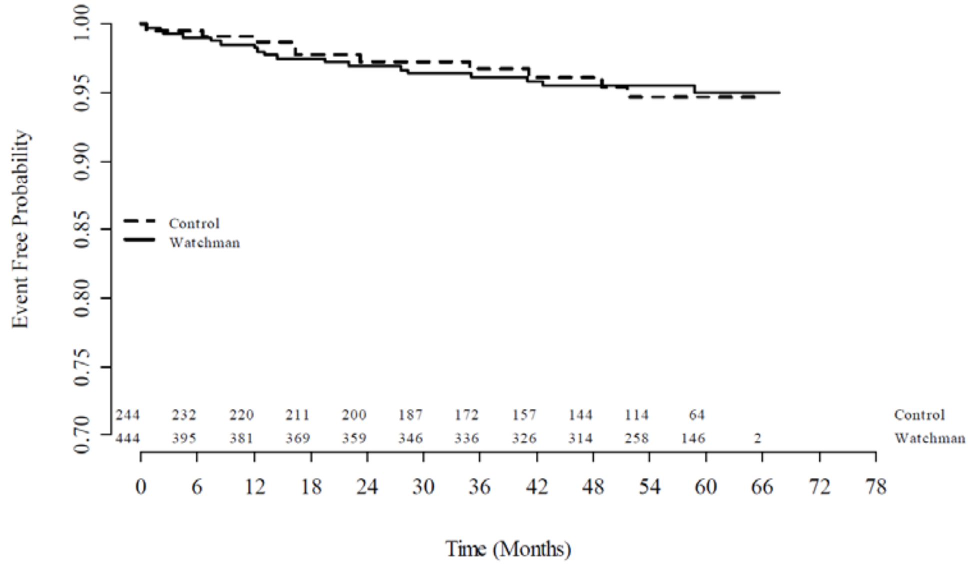


Table 44: Kaplan-Meier Estimates: Freedom from Ischemic Stroke 2621 pt-yrs (Post-Procedure)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	1	1	99.8 (98.4, 100.0)	1	1	99.6 (97.1, 99.9)
6-months	3	4	99.0 (97.5, 99.6)	0	1	99.6 (97.1, 99.9)
1-year	2	6	98.5 (96.8, 99.3)	1	2	99.2 (96.7, 99.8)
2-year	6	12	97.0 (94.7, 98.3)	4	6	97.3 (94.1, 98.8)
3-year	3	15	96.1 (93.6, 97.6)	1	7	96.7 (93.3, 98.4)
4-year	2	17	95.5 (92.9, 97.2)	1	8	96.1 (92.4, 98.1)
5-year	1	18	95.1 (92.2, 96.9)	2	10	94.7 (90.2, 97.2)

Randomization Allocation (2 Device: 1 Control)

FDA Comment: The ITT Kaplan-Meier curve and estimates show no evidence of a late increase in the rate of ischemic strokes in the device group (Figure 7 and Table 43). The Post-Procedure Kaplan-Meier curve and estimates (Figure 8 and Table 44) suggest that once the procedural risk has been accounted for, the ischemic stroke rate in both treatment groups is similar, which is supported by the stroke rate analysis presented in Table 42. The Panel will be asked to comment on the clinical significance of the ischemic stroke analysis in terms of the long-term safety and effectiveness of the WATCHMAN device.

Primary Safety Endpoint

For the 2621 patient-years analysis, the primary safety event rate was 3.6% for the device group and 3.1% for the control group (Table 45). Over time, the difference in the cumulative rate of safety events narrowed between treatment groups with a difference of 1.9% in the 1588 pt-yr analysis and a difference of 0.5% in the 2621 pt-yr analysis.

Table 45: PROTECT AF Primary Safety Results (ITT)

Data Set	Device			Control			Rel. Risk (95% CrI)
	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	
1588 pt-yrs	463	54/979.9	5.5 (4.2, 7.1)	244	20/554.6	3.6 (2.2, 5.3)	1.53 (0.95, 2.70)
2621 pt-yrs	463	60/1666.2	3.6 (2.8, 4.6)	244	27/878.5	3.1 (2.0, 4.3)	1.17 (0.78, 1.96)

The Kaplan-Meier curve and estimates for the Primary Safety Endpoint ITT analysis are included in Figure 9 and Table 46, respectively.

Figure 9: Kaplan-Meier Curve: Freedom from Primary Safety Event 2621 pt-yrs (ITT)

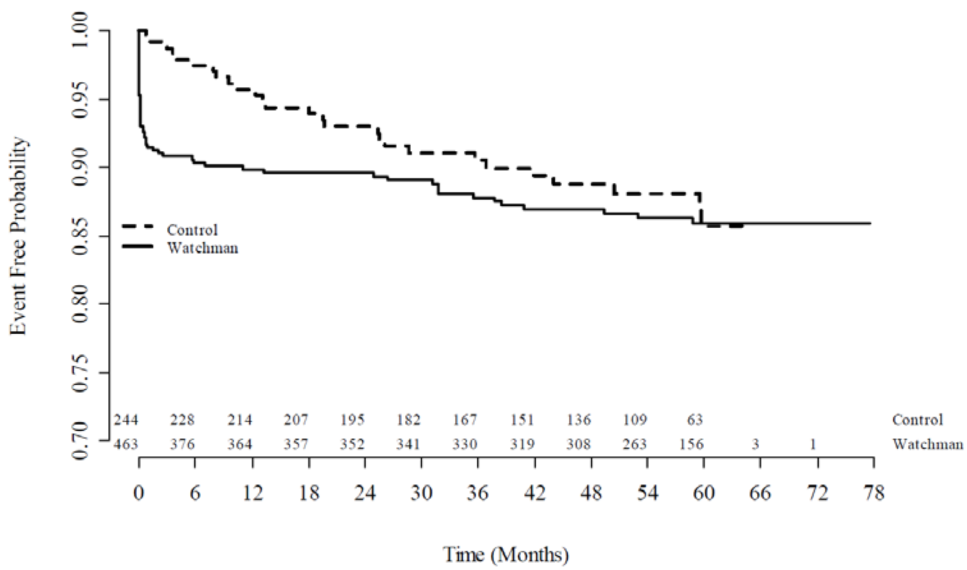


Table 46: Kaplan-Meier Estimates: Freedom from Primary Safety Event 2621 pt-yrs (ITT)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	32	32	93.1 (90.3, 95.0)	0	0	100.0 (100.0, 100.0)
45-days	7	39	91.5 (88.6, 93.7)	2	2	99.2 (96.7, 99.8)
6-months	5	44	90.3 (87.2, 92.7)	4	6	97.5 (94.5, 98.9)
1-year	2	46	89.9 (86.7, 92.3)	4	10	95.7 (92.2, 97.7)
2-year	1	47	89.6 (86.4, 92.1)	6	16	93.0 (88.8, 95.7)
3-year	7	54	87.8 (84.3, 90.5)	5	21	90.5 (85.8, 93.7)
4-year	3	57	87.0 (83.4, 89.8)	3	24	88.8 (83.7, 92.4)
5-year	3	60	85.9 (82.2, 88.9)	3	27	85.7 (79.3, 90.3)

Randomization Allocation (2 Device: 1 Control)

The sponsor also presented the number and rate of the various types of safety events (Table 47). The safety events of interest included pericardial effusion requiring drainage, cranial bleeding events, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitated an operation.

Table 47: Primary Safety Events by Event Type (ITT)

	Device		Control	
Type	**N Events**	**% of Randomized Subjects**	**N Events**	**% of Randomized Subjects**
Gastrointestinal Bleeding	14	3.0%	16	6.6%
Pericardial Effusion with Cardiac Tamponade	12	2.6%	0	0.0%
Cardiac Perforation	7	1.5%	0	0.0%
Stroke - Ischemic	6	1.3%	0	0.0%
Cranial Bleed	4	0.9%	1	0.4%
Device Embolization	3	0.6%	0	0.0%
Stroke - Hemorrhagic	3	0.6%	9	3.7%
Other Study Related	3	0.6%	0	0.0%
Pericardial Effusion-Serious	3	0.6%	0	0.0%
Major Bleed Requiring Transfusion	2	0.4%	0	0.0%
Bruising - Hematoma	1	0.2%	0	0.0%
Epistaxis	1	0.2%	0	0.0%
Arrhythmias (temporary asystole)	1	0.2%	0	0.0%
Anemia Requiring Transfusion	0	0.0%	1	0.4%

Randomization Allocation (2 Device: 1 Control)

FDA Comment: As would be expected, device implantation (which requires an invasive cardiovascular procedure) was associated with a higher rate of safety events versus the control group. There does not appear to be a long-term increase in the number of safety events.

Major Bleeding

The rate of major bleeding within 45 days (when device group subjects were still receiving warfarin) was 9.1% in the device group versus 6.7% in the control group. Beyond 6 months (when over 90% of implanted subjects had discontinued warfarin therapy), the rate of major bleeding was 0.9% in the device group versus 2.8% in the control group (Table 48).

Table 48: PROTECT AF Major Bleeding Results

Event	Device		Control		P-Value
	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs) (95% CI)	
Major bleeding	50/463 (10.8%)	3.0 (50/1679.1) (2.3,3.9)	27/244 (11.1%)	3.1 (27/878.2) (2.1,4.5)	0.894
Procedure related major bleeding	28/463 (6.0%)	NA	NA	NA	NA
Non-procedure related major bleeding	23/463 (5.0%)	1.3 (23/1738.2) (0.9,2.0)	27/244 (11.1%)	3.1 (27/878.2) (2.1,4.5)	0.0030
0-45 days	5/463 (1.1%)	9.1 (5/54.7) (3.8, 22.0)	2/244 (0.8%)	6.7 (2/29.7) (1.7, 27.0)	0.7151
45days – 6 months	4/432 (0.9%)	2.6 (4/153.6) (1.0, 6.9)	4/239 (1.7%)	4.6 (4/87.8) (1.7, 12.1)	0.4285
Beyond 6 months	14/397 (3.5%)	0.9 (14/1529.9) (0.5, 1.6)	21/228 (9.2%)	2.8 (21/760.7) (1.8, 4.2)	0.0014

FDA Comment: A postulated benefit of the WATCHMAN device compared with anticoagulation therapy is a reduced rate of bleeding events that would emerge in device subjects subsequent to the procedure and after warfarin was discontinued. Table 48 demonstrates a numerical trend consistent with this hypothesis. However, PROTECT AF was not designed or specifically powered to detect a difference in bleeding rates between WATCHMAN device and control subjects. The absence of a signal of reduced bleeding complications in PREVAIL should be considered in evaluation the bleeding rates observed in PROTECT AF.

7.2 CONTINUED ACCESS TO PROTECT AF (CAP) REGISTRY

Study Name: Continued Access to PROTECT AF (CAP)

Study Objective: To allow continued access to the WATCHMAN device after the completion of enrollment in PROTECT AF during the preparation and evaluation of the PMA (P080022) for the WATCHMAN device.

Study Design: Prospective, multicenter, non-randomized single arm continued access registry.

Subjects and Investigational Sites: A total of 566 subjects were enrolled at 26 investigational sites (24 U.S. and 2 European).

Treatment: Subjects underwent WATCHMAN device implantation into the LAA via atrial transseptal access plus short-term (45-day, window ≤60 days) warfarin therapy. Subjects were assessed 45 days post-procedure, and if a TEE demonstrated complete LAA occlusion, warfarin therapy could be discontinued. Continuation of warfarin was at the discretion of the treating physician. If warfarin was discontinued, subjects remained on clopidogrel through 6 months post-device implantation and aspirin indefinitely.

Follow up Schedule: All enrolled subjects were required to receive follow-up assessments to re-assess medical status and evaluate for the occurrence of adverse events according to the schedule in Table 49. The follow-up schedule is very similar to the follow-up schedules for PROTECT AF and PREVAIL. The most notable difference is that CAP subjects were not required to have a TEE at 6 months if the LAA was determined to be closed at 45 days.

Table 49: CAP Follow-up Requirements

Study Requirements	**45-day follow-up**	**6-month follow-up** (via telephone or office per protocol)	**9-month follow-up** (via telephone)	**12-month follow-up**	**18-month and Semi-annual telephone follow-up**	**24-month and Annual office follow-up**
TEE	√	If required		√		
INR[a]	√	√	Monthly if required	Monthly if required	Monthly if required	Monthly if required
Resting Heart Rate SBP and DBP	√			√		√
Neurological Assessment[b]				√		√
NIH Stroke Scale	√			√		√
Barthel Index (BI)	√	√	√	√	√	√
Modified Rankin Scale (MRS)	√	√	√	√	√	√
SF-12v2 Health Survey				√		

[a] INR checks required every other week through 45-Day Follow-up Visit. If a subject continues warfarin beyond 45-Day visit, INR checks should be done every other week through 6 months and monthly thereafter if required.
[b] Neurological assessment by neurologist; required at 12 and 24 months.

Inclusion/Exclusion Criteria: The inclusion and exclusion criteria were identical to PROTECT AF.

Endpoints: The endpoints for CAP were identical to PROTECT AF.

Statistical Analysis: The primary analysis included all enrolled subjects. There were no pre-specified hypotheses; descriptive statistics were used to present the results.

CAP RESULTS

Subject Accountability

A total of 566 subjects were enrolled at 24 U.S. and 2 European sites. All enrolled subjects had a device implant attempt and 534/566 (94.3%) subjects had a successful implant attempt.

Subject Demographics and Baseline Characteristics

The distribution of baseline demographics and risk factors was similar to that of the PROTECT AF subjects (Table 50). Similar to PROTECT AF, the study population was predominantly male (~65%).

Table 50: CAP Registry Baseline Demographics and Risk Factors

Characteristic		Mean±SD (N) Min, Max or N/Total (%)
Age (years)		74.0 ± 8.3 (566) 44.0, 94.0
Height (inches)		68.2 ± 4.2 (566) 57.0, 79.0
Weight (lbs)		193.5 ± 45.2 (565) 91.0, 349.0
Gender	Female	195/566 (34.5%)
	Male	371/566 (65.5%)
$CHADS_2$ Score (Categorical)		
	1	132/566 (23.3%)
	2	200/566 (35.2%)
	3	120/566 (21.2%)
	4	78/566 (13.8%)
	5	32/566 (5.7%)
	6	4/566 (0.7%)
$CHADS_2$ Score (Continuous)		2.5 ± 1.2 (565) 1.0, 6.0
CHA_2DS_2-VASc Score (Categorical)		
	1	24/564 (4.3%)
	2	80/564 (14.2%)
	3	163/564 (28.9%)
	4	143/564 (25.4%)
	5	88/564 (15.6%)
	6	46/564 (8.2%)
	7	17/564 (3.0%)
	8	1/564 (0.2%)
	9	1/564 (0.2%)
CHA_2DS_2-VASc Score (Continuous)		3.7 ± 1.4 (564) 0.0, 9.0
Risk Factors		
	CHF	108/566 (19.1%)
	Hypertension	502/565 (88.8%)
	Diabetes	141/566 (24.9%)
	Stroke/TIA	172/566 (30.4%)
	Previous MI	79/566 (14.0%)
	LVEF 40% or Less	43/565 (7.6%)
	Age <65	61/566 (10.8%)
	Age 65-75	212/566 (37.5%)
	Age >75	293/566 (51.8%)

Follow-up and Subject Withdrawal

The mean follow-up time was 28.6 ± 10.6 months. Approximately 20% (110/566) of enrolled subjects have exited the study early (Table 51). Of the 534 subjects in whom the device was implanted, approximately 85% (458/534) have completed follow-up to two years.

Table 51: CAP Registry Subject End of Study Summary

Discontinuation Reason	Total N/566 (%)
No Device Implanted	32 (5.7%)
Death	53 (9.4%)
Lost to Follow-up	10 (1.8%)
Subject Consent Withdrawn	10 (1.8%)
Other	5 (0.9%)

Primary Effectiveness Endpoint

The primary analysis dataset included a total of 1328.1 patient-years. The event rate for the primary effectiveness endpoint was 2.0 per 100 patient-years with a 95% confidence interval of 1.4 to 3.0 (Table 52). A total of 27 events contributed to this endpoint, which included 14 ischemic strokes, 11 cardiovascular or unexplained deaths, 1 hemorrhagic stroke, and 1 systemic embolism (Table 53).

Table 52: CAP Primary Effectiveness Results

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	(95% CI)
Primary Effectiveness	2.0 (27/1328.1)	1.4, 3.0

Table 53: Events Contributing to Primary Effectiveness Endpoint

Event Type	N Events	% of Subjects
Stroke - Ischemic	14	2.5%
Death (Cardiovascular or Unexplained)	11	1.9%
Stroke - Hemorrhagic	1	0.2%
Systemic Embolism	1	0.2%

FDA Comment: The rates of the individual components of the primary effectiveness endpoint (Table 53) are numerically lower than those observed in the device group of PROTECT AF. Notably, the ischemic stroke rate was lower in the CAP than in the device group of PROTECT AF (2.5% versus 5.2%).

The Kaplan-Meier curve and estimates for the Primary Effectiveness analysis are shown in Figure 10 and Table 54, respectively.

Figure 10: Kaplan-Meier Curve: Freedom From Primary Effectiveness Endpoint Event

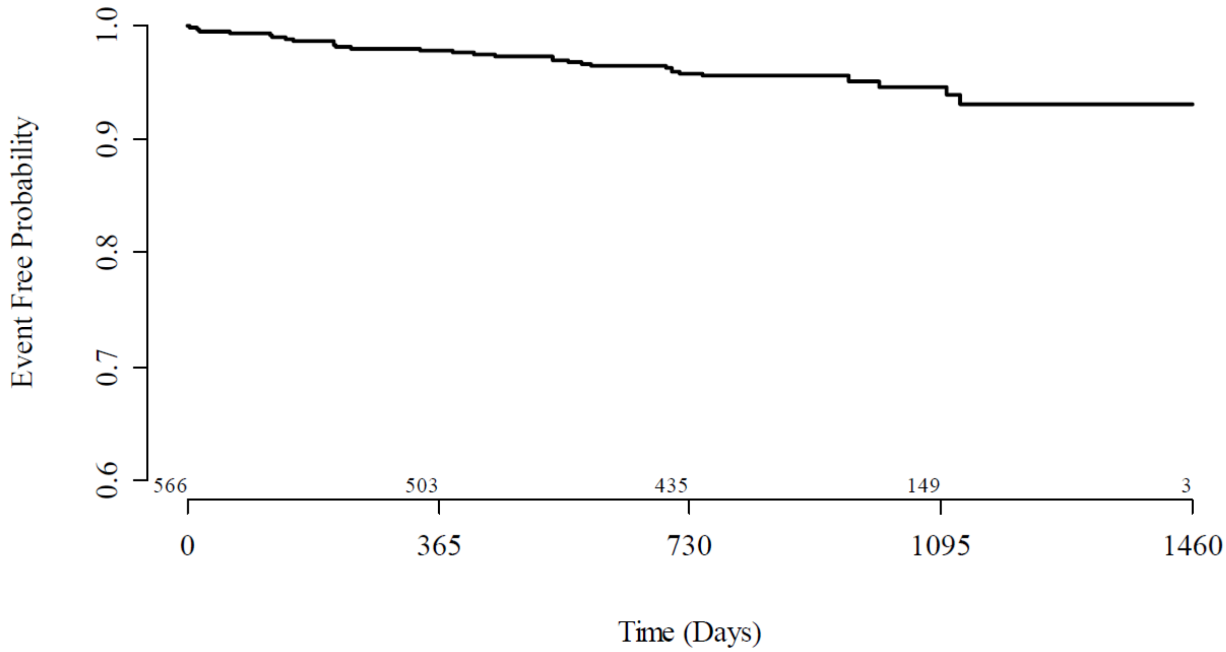


Table 54: Kaplan-Meier Estimates: Freedom from Primary Effectiveness Event

Time Point	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.8
45-days	2	3	99.5
6-months	5	8	98.5
1-year	4	12	97.8
2-year	10	22	95.7
3-year	3	25	94.6
4-year	2	27	93.1

Primary Safety Endpoint

The primary safety event rate was 4.3 per 100 patient-years (Table 55). Half (27/54) of the events were gastrointestinal bleeding events (GI bleeds) requiring either transfusion of at least two units of blood or surgical intervention (Table 56). None of the safety endpoint GI bleeds were related to the implant procedure, and all occurred more than 7 days after implant attempt. Of the 27 GI bleeds, 10 occurred within the first 45 days and 6 occurred between 45 days and 6 months, while subjects were either taking warfarin or dual antiplatelet (clopidogrel plus aspirin) therapy.

Table 55: CAP Primary Safety Endpoint Results

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	(95% CI)
Primary Safety	4.3 (54/1242.3)	3.3, 5.7

Table 56: Primary Safety Events by Event Type

Event Type	N Events	% of Subjects
Gastrointestinal Bleeding	27	4.8%
Pericardial Effusion with Cardiac Tamponade	7	1.2%
Other Study Related	5	0.9%
Major Bleed Requiring Transfusion	4	0.7%
Pseudoaneurysm	2	0.4%
Ventricular Tachyarrhythmia	2	0.4%
Anemia Requiring Transfusion	1	0.2%
Cardiac Perforation	1	0.2%
Device Embolization	1	0.2%
Prolonged Bleeding from a Laceration	1	0.2%
Rectal Bleeding	1	0.2%
Stroke - Hemorrhagic	1	0.2%
Stroke – Ischemic	1	0.2%

FDA Comment: No new safety issues were identified in the CAP registry.

The Kaplan-Meier curve and estimates for the Primary Safety Endpoint ITT analysis are included in Figure 11 and Table 57, respectively.

Figure 11: Kaplan-Meier Curve: Freedom From Safety Endpoint Event

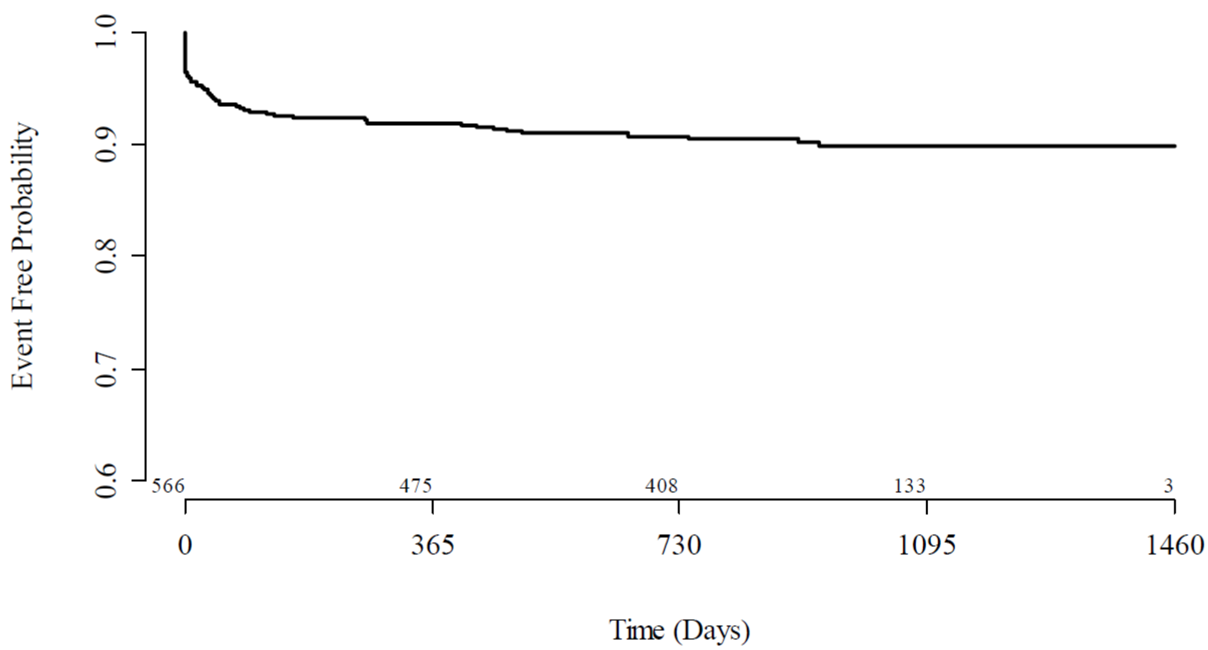


Table 57: Kaplan-Meier Estimates: Freedom from Primary Safety Endpoint

Time Point	N Events	N Cumulative Events	Event Free Rate (%)
7-days	24	24	95.8
45-days	11	35	93.8
6-months	8	43	92.3
1-year	2	45	91.9
2-year	6	51	90.7
3-year	3	54	89.8
4-year	0	54	89.8

Warfarin Discontinuation

The percentage of successfully implanted device group subjects who were able to discontinue warfarin at 45 days post-procedure was 95.8% (507/529, Table 58).

Table 58: Warfarin Discontinuation – Successfully Implanted Subjects

Visit	N/Total (%)
45 Day	507/529 (95.8%)
6 Month	493/500 (98.6%)
12 Month	455/472 (96.4%)

FDA Comment: The percentage of successfully implanted CAP subjects who were able to discontinue warfarin at 45 days post-procedure (95.8%) was greater than the percentage observed in PROTECT AF (86.8%) and PREVAIL (92%).

8 POST APPROVAL STUDY (PAS)

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the WATCHMAN device is approved, a PAS should be required as a condition of approval for this first-of-a-kind device. Based on a review of the premarket data, FDA has identified the following reasons for conducting a post-approval study:

Assess the 5-year long-term performance of the device
The PREVAIL trial was designed to address limitations of the PROTECT AF study. Although the PROTECT AF study has 45-month follow-up data, the PREVAIL study has a mean follow-up time of only 11.8 months data and projected 18-month primary endpoint rates. Furthermore, at the time of the database lock for the primary endpoint assessment (January 16, 2013), only about one third of randomized subjects (72 device subjects and 39 control subjects) had completed their 18-month follow-up. The first and second primary endpoints were calculated from the probability of events occurring at 18 months. Thus, in addition to PROTECT AF data, additional long-term follow-up in a PAS is needed.

Evaluate device performance in patient sub-groups
In the PREVAIL study, baseline covariate $CHADS_2$ scores had statistically significant effects on the first and second primary endpoints. A greater proportion of subjects (8.7%, 4/46) in the higher $CHADS_2$ (4-6 score) subgroup experienced events than subjects in the lower $CHADS_2$ (1-3 score) subgroup (4.5%, 10/223) for the first primary endpoint (HR= 0.28, p = 0.0079). Likewise, a higher baseline $CHADS_2$ score resulted in an increased risk of the second primary endpoint of late ischemic events compared to subjects with lower scores [$CHADS_2$ score (1-3 vs. 4-6), HR=0.11, 0.9% vs. 6.5%, p =0.0117]. Thus, subgroup analysis of the PAS outcomes including, but not limited to, $CHADS_2$ score is recommended to further explore the effect of baseline covariates on clinical outcomes.

The sponsor submitted the PAS protocol proposal dated September 5, 2013. An overview of the proposed PAS protocol is provided below. Concerns about the PAS protocol proposal are included in the assessment following the proposal overview.

OVERVIEW OF THE PROPOSED POST-APPROVAL STUDY

Objectives
To assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN LAAC Therapy in a routine clinical practice.

Study Design and Study Population
This is a non-randomized, single arm study prospectively enrolling subjects newly implanted with the WATCHMAN device and retrospectively enrolling subjects previously implanted with the WATCHMAN device in the Continued Access to PROTECT (CAP), PREVAIL, or Continued Access to PREVAIL (CAP2) clinical studies (IDE G020312).

Study Endpoints and Hypotheses
The study hypothesis for each of the three primary endpoints is stated below.

<u>First primary endpoint hypothesis</u>
The incidence of stroke, cardiovascular death and systemic embolism combined from implant through 18 months is less than the pre-specified performance goal of 11.4%.

<u>Second primary endpoint hypothesis</u>

The incidence of ischemic stroke and systemic embolism through 18 months post implant (excluding the first 7 days implant) is less than the pre-specified performance goal of 6.1%.

<u>Third primary endpoint hypothesis</u>
The incidence of adverse events (composite endpoint of all cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair) from implant through 7 days of the procedure or by hospital discharge, whichever is later, is less than the pre-specified performance goal of 3.7%.

Data Collection Procedures
Screening procedures will not be repeated for subjects retrospectively enrolled from the PREVAIL, CAP, and CAP2 studies (previously treated with the device and still being followed in their respective studies). The following information will be collected at each visit (Table 59):

Table 59: PAS Visit Schedule

Procedure/Assessment	Screening	Implant	45-Day (± 15 Days) Office Visit	1-Year (± 60 Days) Office Visit	18-month, 2-, 3-, 4- and 5- Years (± 60 Days) Telephone Interview
Informed consent	X				
Demographics and medical history	X				
Physical assessment including vital signs	X		X	X	
Transesophageal echocardiogram (TEE)	X	X	X		
Anticoagulant and antiplatelet medications	X		X	X	X
NIH Stroke Scale	X		X	X	
Modified Rankin Scale	X		X	X	X
Device and implant details		X			
Adverse event monitoring		X	X	X	X

Enrollment Plan and Follow-up
Subjects who meet all the inclusion criteria, and none of the exclusion criteria below, who provide written informed consent may be prospectively enrolled into the PAS.

Inclusion Criteria

1. The patient is 18 years of age or older.
2. The patient has non-valvular atrial fibrillation.
3. The patient has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation):
    a. The patient is a female age 75 or older
    b. The patient has a baseline Left Ventricular Ejection Fraction (LVEF) ≥30% and <35%
    c. The patient is age 65-74 and has diabetes or coronary artery disease
    d. The patient is age 65 or greater and has documented congestive heart failure
4. The patient is eligible for post implant warfarin therapy.
5. The patient is willing and capable of providing informed consent and participating in all testing/ visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol.

Exclusion Criteria

1. The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by peri-procedural TEE.
2. The patient has a history of atrial septal repair or has an ASD/PFO device.
3. The patient's LAA anatomy will not accommodate a WATCHMAN device.
4. The patient has any contraindications for other percutaneous catheterization interventions due to patient size (i.e. too small for TEE probe, catheter size, etc.) or condition (i.e. active infection, bleeding disorder, untreated ulcer, etc.).
5. The patient is contraindicated or allergic to aspirin.
6. The patient requires long term warfarin therapy for a condition other than atrial fibrillation.
7. The patient has a life expectancy of less than one year.

Subjects previously implanted with the WATCHMAN device in the CAP, PREVAIL, or CAP2 clinical studies (IDE G020312) that are in active follow-up will be asked to participate in the PAS. The subjects expected to be retrospectively enrolled in the PAS will be considered enrolled after providing written informed consent (not required to meet eligibility criteria).

Enrollment will be conducted over a 2-year period. All subjects will be assigned to the WATCHMAN device group (single arm study). Subjects will be followed at 45 days and 1-year with office visits, then all subjects will complete a telephone interview at 18 months, 2-, 3-, 4- and 5-years post-implant. The follow-up procedures and data collection are stated in Table 56 above.

Study Medication Regimen

Following device placement, warfarin therapy will be adjusted to achieve a therapeutic INR of 2.0 – 3.0. Implanted subjects should be on adjusted dose warfarin therapy through at least the

45-day follow-up transesophageal echocardiogram (TEE). The post implant medication regimen presented in the submission is provided in Table 60 below:

Table 60: PAS Post-Implant Medication Regimen

Interval	Warfarin	Aspirin	Clopidogrel
Implant to 45-Days	Yes Adjusted dose to achieve INR of 2.0 – 3.0	Yes 81mg while on warfarin	No
LAA Seal per 45-Day TEE			
45-Days to 6-Months	**Stop** warfarin	Yes 325mg recommended	Yes, **Start** Clopidogrel 75mg
6-Months to 5 Years	No	Yes 325mg recommended	No, **Stop** Clopidogrel 6 months post implant
No LAA Seal per 45-day TEE			
45-Days to 6-Months	Yes	Yes 81mg while on warfarin	No
6-Months to 5 Years	Discontinue when LAA seal adequate	81mg while on warfarin. If no warfarin therapy, then adult aspirin (325mg) indefinitely	No

Sample size

Up to 1000 patients comprised of up to 600 retrospective and 600 prospective subjects from a maximum of 100 sites in the U.S. will be enrolled. Of the 1000 enrolled patients, 850 are expected to be included in the baseline analysis. About 150 newly enrolled patients are expected to be excluded from all primary endpoint analyses due to the following reasons:

1. Patients with prior stroke or TIA within the 90 days prior to enrollment;
2. Patients who experienced an MI within 90 days prior to enrollment; or
3. Patients with symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke).

These subjects will be excluded from the PAS primary endpoint analyses since patients who met any of these criteria were excluded in the CAP, PREVAIL, or CAP2 studies.

To calculate the sample size of the PAS, the expected event and attrition rates for each primary endpoint stated below were based on the PREVAIL data as of January 16, 2013.

First Primary Endpoint

- Expected event rate = 8.4% (KM Estimate for 2-year 1st Primary Endpoint Rate in the device group)
- Performance goal = 11.4% (8.4% + 3% delta)
- Expected attrition/missing data = 20%
- One-sided significance level = 5%

- Sample size = 850 patients
- Power = 85.4%

The proposal states that a clinically acceptable delta of 3.0% was added to the expected event rate to establish the performance goal of 11.4%.

<u>Second Primary Endpoint</u>

- Expected event rate = 3.9% (KM Estimate for 2-year 2nd Primary Endpoint Rate in the device group)
- Performance goal = 6.1% (3.9% +2.2% delta)
- Expected attrition/missing data = 20%
- One-sided significance level = 5%
- Sample size = 850 patients
- Power = 86%

The proposal states that a clinically acceptable delta of 2.2% was added to the expected event rate to establish the performance goal of 6.1%

<u>Third Primary Endpoint</u>

- Expected event rate = 2.2% (3rd Primary Endpoint rate in the device group)
- Performance goal = 3.7% (2.2% + 1.5% delta)
- Expected attrition/missing data = 0%
- One-sided significance level = 5%
- Sample size = 850 patients
- Power = 81.5%

The proposal states that a clinically acceptable delta of 1.5% was added to the expected event rate to establish the performance goal of 3.7%.

Statistical Plan

Analyses will include all subjects enrolled into the study who undergo an attempted implant of the WATCHMAN device. For time-to-event analyses, all subjects not having an event or who are lost to follow-up will be censored at the time of the last documented follow-up visit.

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected.

For the first and secondary primary endpoints, event rate from implant through 18 months post-implant will be calculated using Kaplan-Meier analysis. The 95% one-sided upper pointwise confidence limit of the event rate will be calculated using log-log methodology for all eligible subjects contributing to the analyses and compared to the respective performance goal. Null hypotheses will be rejected if the respective upper confidence limit is less than the performance goal.

For the third primary endpoint, an exact binomial test will be used to test if the event rate is less than the pre-specified performance goal of 3.7%. The null hypothesis will be rejected if the p-value from the exact binomial test is less than 0.05.

Poolability Analysis
A pooling analysis will be conducted for each primary endpoint to confirm the poolability of retrospective and prospective patients. A logistic regression model to adjust for imbalance between baseline covariates will include baseline covariates such as $CHADS_2$ score, age, gender, AF category, left atrium size, implanted device size, left ventricular ejection fraction, and new vs. experienced operator.

A likelihood ratio test, at a 10% significance level, will be used to compare the log likelihoods between a model containing enrollment type (retrospective vs. prospective) as a covariate and a model not containing enrollment type as a covariate. For each endpoint in which a difference between enrollment type is found, the endpoint results for each enrollment type will be calculated and presented separately.

Timeline
The timeline for study implementation was not provided with the submission.

<u>FDA Comments on Proposed Post Approval Study</u>

Study Objectives
The proposed PAS is intended to assess long-term safety and effectiveness outcomes associated with the use and implantation of the WATCHMAN device in real-world use. The proposed follow-up period of 5 years is expected to provide adequate data for long-term safety and effectiveness assessment.

Study Design
Patients previously treated with the WATCHMAN device will be retrospectively enrolled and newly implanted patients will be prospectively enrolled. Thus, the decision to conduct a poolability analysis for the primary endpoints is appropriate. The plan to enroll all previously implanted patients in active follow-up (not completed 5-year visit or withdrawn) who provide written informed consent will help avoid sampling bias but may increase self-selection bias as not all patients may be willing to re-consent.

The sponsor proposed to use projected event rates from the PREVAIL study plus a specified delta as performance goals for the PAS primary endpoints. No justifications were provided for the delta values used in the calculations of the performance goals. Considering that the PAS population will partly include PREVAIL study subjects, from whom the performance goals were derived, it is unclear how inclusion of PREVAIL subjects in the PAS may impact the PAS outcomes and comparisons to the performance goals.

The PAS population will include active subjects from the Continued Access to PROTECT (CAP) Registry, PREVAIL study, Continued Access to PREVAIL (CAP 2) Registry, and newly enrolled subjects. In the latter three studies, subjects with $CHADS_2$=1 score could only be enrolled if the subject is female age 75 or older, has baseline LVEF > 30% and < 35%, age 65-74 years with diabetes or coronary artery disease, or age 65 or older with documented congestive heart failure. However, the CAP Registry study cohort included $CHADS_2$=1 subjects (23.7% of the device group) who were not required to meet these aforementioned criteria and who were at low risk for stroke. These CAP patients could be eligible for aspirin therapy (per the ACC/AHA/ESC 2006 Practice Guidelines for the Management of Patients With Atrial Fibrillation). Enrolling subjects from the CAP registry whose population include subjects with $CHADS_2$=1 score who were at low risk for stroke into the PAS could bias the results in favor of the device meeting the performance goals.

FDA Comment: The Panel will be asked to discuss the appropriateness of enrolling subjects from the CAP registry in the PAS.

In both PROTECT AF and PREVAIL trials, the clinical outcomes after implantation of the WATCHMAN device were compared to warfarin therapy. There are three novel anticoagulants that have been approved as alternatives to warfarin in patients with non-valvular AF. The proposed PAS results for the primary endpoints will be compared to performance goals derived from projected event rates observed in the PREVAIL trial device group.

FDA Comment: The Panel will be asked to discuss the appropriateness of the proposed single arm study design and performance goals.

Sample Size

The expected event and attrition rates used in the calculation of sample size were based on the PREVAIL study results. The assumed rates for the first primary endpoint (8.4%) and second primary endpoint (3.9%) were 2-year projections from the premarket results. The assumed rate for the third primary endpoint (2.2%) was the event rate observed for that endpoint in premarket study. The expected event rates, sample size and power calculations are preliminary, and will be re-evaluated when the appropriate comparison is decided on based on the Panel's input.

Of the total expected enrollment of 1000 patients the sponsor indicated that 150 patients who meet certain exclusion criteria will be excluded from the primary endpoint analysis. Since patients who met those specific exclusion criteria do not exist in the CAP, PREVAIL, or CAP2 study population, these 150 patients can only be excluded for the newly enrolled cohort. This reduces the newly enrolled cohort to 450 patients for endpoint analyses. Clarification is needed regarding the number of newly enrolled subjects expected to be included in the analysis of the primary endpoints.

Follow–up Procedures

Given that two of the three primary endpoints are planned for evaluation at 18 months, it is recommended that: (1) the 18- month evaluation include physical examination and NIH stroke scale assessment as planned for 45 days and 1 year evaluations; and (2) the 18 months assessment be performed as office visit and not via telephone interviews.

Outcomes

The PAS will include enrollment of subjects newly implanted with the device. However, the third primary endpoint of the study does not capture all procedure-related endpoints such as defined procedure success, device recaptures, and device malfunctions. These endpoints are needed to assess device and procedural performance.

Statistical plan
For the first and second primary endpoints, the proposal to use Kaplan-Meier survival analysis with a 95% one-sided confidence limit to test the null hypothesis is appropriate as these are time-to-event assessments.

For the third primary endpoint, the use of one-sided exact binomial test to test the null hypothesis is appropriate as the endpoint will be evaluated as occurrence of an event (proportion) at a timepoint. However, the proposal does not detail how missing covariates or outcomes will be addressed in the analysis.

The statistical analysis plan does not discuss how study endpoints will be reported beyond 18 months post implant. Discussion of statistical analyses for endpoint reporting after 18 months through 5 years needs to be included in the protocol.

The proposal does not include a plan for subgroup analyses. Considering that patients with higher $CHADS_2$ scores (cardiac failure, hypertension, age, diabetes, and stroke) experienced a higher rate of ischemic events than patients with lower $CHADS_2$ scores, subgroup analyses of the PAS outcomes including but not limited to $CHADS_2$ scores is recommended.

9 FDA CONSIDERATIONS AND CONCLUSIONS

Fundamentally, the PREVAIL and PROTECT AF trials were both designed to compare two treatment strategies:

1. WATCHMAN device implantation, 45 days of warfarin plus 81mg aspirin through 45 days post-implantation, followed by 325 mg aspirin plus 75 mg clopidogrel through 6 months post-implantation, followed by indefinite use of 325 mg aspirin; vs.
2. Chronic warfarin therapy.

The clinical question linked to the performance of the WATCHMAN device is whether the study data support stopping warfarin after satisfactory implantation of the device. That is, does implantation of the WATCHMAN device provide equivalent protection against thromboembolic events compared to warfarin in subjects with non-valvular atrial fibrillation?

When evaluating whether the totality of the data (including PREVAIL, PROTECT AF, and the CAP registry) provide a reasonable assurance of safety and effectiveness of the WATCHMAN device for the proposed indications, the following points should be considered:

1. Because the mean subject follow-up in PREVAIL was 11.8 months, there are limited long-term data available from this trial. Additional long-term follow-up data from the PROTECT AF and CAP studies were presented in this PMA. However, the previous

PMA submission was deemed Not Approvable because of issues with the conduct and execution of the PROTECT AF trial, and FDA requested a new prospective trial.

2. Study success for PREVAIL required that the non-inferiority criteria be met for both the first and second primary endpoints. The non-inferiority criterion was not met for the first primary endpoint in PREVAIL, as the upper bound of the 95% credible interval for the 18-month rate ratio (1.89) exceeded the non-inferiority margin of 1.75. Although one of the two non-inferiority criteria were met for the second primary endpoint, there were few endpoint events (5 ischemic strokes in the device group and 1 in the control group), which numerically favored the control group.

3. A Bayesian approach using 50% discounted historical data from PROTECT AF as prior information was used for the primary analysis of the first and second primary endpoints of PREVAIL. Even after discounting, these prior data have a noticeable influence on the study results for these two primary endpoints. Hence, an examination of the appropriateness of model assumptions is critical in considering the Bayesian results.

4. Procedural safety and procedural learning curve were concerns raised in the previous review of the WATCHMAN device. The PREVAIL study required 25% of subjects to be enrolled by new operators and 20% at new investigational sites These criteria were exceeded, with approximately 40% of subjects enrolled by new operators and/or new sites. Importantly, device implantation by new operators was not associated with reduced rates of implant success or an increased risk of major adverse events. The current experience suggests that a robust training program is effective in reducing the risk of peri-procedural complications.

5. Over the last three years, three novel anticoagulants (NOACs) have been FDA-approved based on large randomized trials vs. warfarin, the historical stand of care. These novel agents are as effective or superior to warfarin in for patients with non-valvular AF. None of the NOACs has been directly compared to the WATCHMAN device. However, even with the availability of the NOACs, warfarin is still widely used in clinical practice in the U.S. and remains an acceptable therapy in patients with non-valvular AF.

The data presented in the PMA characterize the safety and effectiveness of the WATCHMAN LAAC Therapy when used to treat patients with non-valvular atrial fibrillation who are eligible for warfarin therapy. The Advisory Panel will be asked to assess whether these data demonstrate a reasonable assurance of safety and effectiveness and address the benefit-risk profile of the WATCHMAN device for the prevention of stroke and systemic embolism in these patients. It is critical that Advisory Panel members review the totality of data in making these determinations.

Appendix A – PROTECT AF Study Design and Previous Results

Study Name: WATCHMAN LAA Closure Technology for Embolic PROTECTion in Patients with Atrial Fibrillation (PROTECT AF)

Study Objective: To demonstrate the safety and effectiveness of the WATCHMAN device for the prevention of ischemic stroke and systemic thromboembolism in subjects with non-valvular atrial fibrillation who require treatment for potential thrombus formation and who are eligible for warfarin therapy.

Study Design: Prospective, multicenter, randomized controlled trial comparing device implantation plus short-term (45-days) warfarin therapy (WATCHMAN) to warfarin therapy (Control).

Randomization Scheme: A 2:1 randomization ratio (Device: Control) was used with stratification by center.

Subjects and Investigational Sites: A total of 800 subjects were enrolled at 59 investigational sites (55 U.S. and 4 European).

Treatment Groups:

Device Placement plus Short Term (45-day, window ≤60 days) Warfarin Therapy (device group): Permanent placement of the device into the LAA using a transseptal puncture technique. Subjects were assessed at 45 days post-procedure, and if a TEE demonstrated complete LAA occlusion, warfarin therapy could be discontinued. Continuation of warfarin was at the discretion of the treating physician. If warfarin was discontinued, subjects remained on clopidogrel for 6 months and aspirin for the duration of the trial.

Anticoagulation Therapy (control group): An inclusion criterion specified that all subjects must either be on warfarin or candidates for warfarin therapy. It was planned that warfarin therapy would be initiated or that subjects would remain on warfarin therapy (target INR = 2.0-3.0) for the duration of the trial.

Follow-up Schedule: All enrolled subjects in both groups were required to receive follow-up assessments to re-assess medical status and evaluate for the occurrence of adverse events. Assessments were made according to the schedule in Table 61.

Table 61: PROTECT AF Follow-Up Requirements

Study Requirements	Baseline	45-Day Follow-up	6-Month Follow-up	9-Month Follow-up (via telephone updates)	12-Month and Annual Follow-up	Semi-Annual Follow-up (via telephone updates)
Device Group:						
TEE	√	√	√		√	
TTE	√					
INR[a]	√	√	Monthly if required	Monthly if required	Monthly if required	Monthly if required
Control Group:						
TEE	√					
TTE	√					
INR[a]	√	√	√	√	√	√
All Enrolled Subjects:						
Resting Heart Rate, Blood Pressure	√	√			√	
Neurological Assessment[b]	√				√[c]	
NIH Stroke Scale[d]	√	√	√		√	
Barthel Index (BI)[e]	√	√	√	√	√	√
Modified Rankin Scale (MRS)[e]	√	√	√	√	√	√
SF-12v2 Health Survey	√				√[f]	
Brain Imaging (CT/MRI) and Stroke Scales[g]	√	As needed	As needed	As needed	As needed	As needed

[a] For WATCHMAN subjects, INR checks required every other week through 45-Day Follow-up Visit. If WATCHMAN subjects continue warfarin beyond 45-Day visit, INR checks should be done every other week through 6 months and monthly thereafter if required. For control subjects, INR should be obtained every other week from randomization until 6 months and monthly thereafter.

[b] Neurological assessment by neurologist.

[c] At 12 and 24 months only.

[d] Neurological consult required if the NIHSS score increases ≥ 2 points from previous visit.

[e] Neurological consult required if the BI decreases ≥ 15 points or the MRS increases ≥1 point from the previous assessment, and the increase/decrease is NOT attributed to a non-neurological cause

[f] At 12 months only

[g] Following a stroke or TIA event including neurological assessment by a Neurologist.

Inclusion/Exclusion Criteria:

Selected Inclusion Criteria

1. 18 years of age or older
2. Paroxysmal (with appropriate documentation) persistent, or permanent non-valvular atrial fibrillation
3. Eligible for long-term warfarin therapy
4. Eligible to come off warfarin therapy if the LAA is sealed, i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice
5. $CHADS_2$ score of 1 or greater

Selected Exclusion Criteria
Clinical (pre-echocardiography) Exclusion Criteria:

1. New York Heart Association Class IV congestive heart failure
2. MI within 3 months
3. Subject had a single occurrence of AF
4. Ablation procedure planned within 30 days of potential WATCHMAN device implant
5. Resting heart rate >110 bpm
6. Transient case of AF (e.g., secondary to recent CABG within 3 months)
7. Symptomatic carotid disease (i.e., carotid stenosis >50% associated with ipsilateral transient symptoms or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs, or ipsilateral stroke within 6 months)
8. Embolic stroke or TIA within the last 30 days
9. Subject requires long-term warfarin therapy:
   - Secondary to conditions such as prior arterial embolism or other indications such as pulmonary embolism or deep vein thrombosis within the previous 6 months
   - Presence of a hypercoagulable state; subject excluded if per medical record documentation, any of the following was present:
     1. Thrombosis occurring at a young age (i.e., less than 40 y/o)
     2. Idiopathic or recurrent venous thromboembolism (VTE)
     3. Thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, IVC, mesenteric veins)
     4. Family history of VTE or of inherited prothrombotic disorder
     5. Recurrence/extension of thrombosis while adequately anti-coagulated
10. Subject is contraindicated for warfarin therapy
11. Subject is contraindicated for aspirin

Echocardiographic Exclusion Criteria (as assessed via TTE and TEE):

1. LVEF <30%
2. Intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
3. High risk patent foramen ovale
4. Significant mitral valve stenosis (i.e., MV area <1.5 cm^2)
5. Existing pericardial effusion of >2 ±1 mm
6. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch
7. Cardiac tumor

Endpoints:

Primary effectiveness endpoint: Successful treatment of the randomized subject without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism.

Primary safety endpoint: Treatment of the subject without the occurrence of life-threatening events as determined by the CEC, which would include events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

Primary technical endpoint: Device success, defined as successful delivery and release of the WATCHMAN implant into the LAA, including successful re-capture and retrieval if necessary.

Additional Analyses

In addition to the primary ITT analysis, the sponsor defined two additional secondary analysis populations: Post-Procedure and Per-Protocol.

- The Post-Procedure analysis excludes any subject with an adverse event that occurred either before or on the date of device implant.
- The Per-Protocol analysis excluded device subjects who did not receive the device or who did not discontinue warfarin therapy, and control subjects for which there was no evidence of warfarin use at either baseline or 45 days.

Statistical Analysis and Hypothesis

The primary analysis is ITT.

A formal hypothesis was established only for the primary effectiveness endpoint. The primary safety endpoint and primary technical endpoints were to be presented as observed rates and confidence intervals; no formal statistical comparisons between groups were planned.

A Bayesian approach based on a Poisson-Gamma model was established to evaluate the primary endpoint (see Appendix B for a brief summary of Bayesian statistics). The number of events was assumed to follow a Poisson distribution with a parameter, λ (hazard rate). In the PROTECT AF study design, λ was assumed to be a constant during any follow-up period. In the Bayesian analysis, a non-informative prior distribution (Γ (0.001, 0.001)) was assumed for λ, so there were no historical data borrowed from other studies.

The statistical analysis plan called for initial interim evaluation after 600 patient-years of follow-up, with subsequent interim evaluations after each additional 150 patient-years, up to a maximum of 1,500 patient years of follow-up. After the first interim analysis, the trial was formally stopped because non-inferiority had been demonstrated according to the predefined stopping rules at 600 patient-years.

Criteria for Non-inferiority: Non-inferiority would be declared if the posterior probability that the event rate for the device group is less than 2 times the event rate for the control group was at least 0.975, and the criterion for futility was not met.

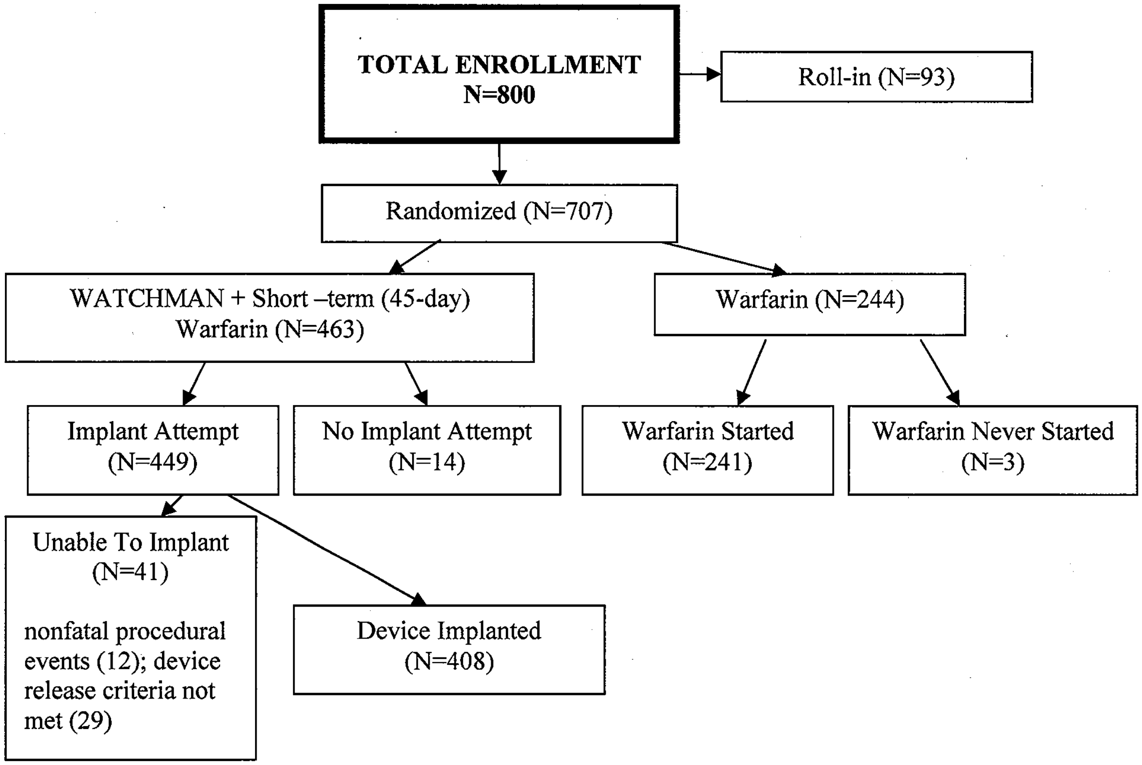
Criterion for Superiority: Superiority would be declared if the posterior probability that the event rate for the device group is less than the event rate for the control group was at least 0.95. The superiority test was to be performed only if non-inferiority could be established.

PROTECT AF RESULTS

Subject Accountability

A total of 800 subjects were enrolled at 59 sites (55 U.S. and 4 European). Total enrollment included 463 subjects randomized to the device group, 244 subjects randomized to the control group, and 93 roll-in subjects. Subject accountability is summarized in Figure 12.

Figure 12: PROTECT AF Subject Accountability



Subject Demographics and Baseline Characteristics

Two sample t-tests or chi-square tests, as appropriate, were used to compare the baseline demographics of the randomized groups (Table 62). Baseline demographic analyses showed no significant differences between the treatment and control groups. The study population was predominately male (~70%) and overwhelmingly Caucasian (~91%).

Table 62: PROTECT AF Baseline Demographics

Characteristic	Device N=463	Control N=244	P-value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	72.7 ± 9.2 (244) (41.0, 95.0)	0.179
Height (inches)	68.2 ± 4.2 (462) (54.0, 82.0)	68.4 ± 4.2 (244) (59.0, 78.0)	0.607
Weight (lbs)	195.3 ± 44.4 (463) (85.0, 376.0)	194.6 ± 43.1 (244) (105.0, 312.0	0.834
Gender			0.928
Female	137/463 (29.6%)	73/244 (29.9%)	
Male	326/463 (70.4%)	171/244 (70.1%)	
Race/Ethnicity			0.779
Asian	4/463 (0.9%)	1/244 (0.4%)	
Black/African American	6/463 (1.3%)	5/244 (2.0%)	
Caucasian	425/463 (91.8%)	222/244 (91.0%)	
Hispanic/Latino	25/463 (5.4%)	15/244 (6.1%)	
Hawaiian/Pacific Islander	1/463 (0.2%)	1/244 (0.4%)	
Other	2/463 (0.4%)	0/244 (0.0%)	

Two sample t-tests or chi-square tests, as appropriate, were used to compare the baseline risk factors for the randomized groups (Table 63). Although many baseline risk factors in the control group were noted at a slightly higher frequency, there were no statistically significant differences between the treatment and control groups.

Table 63: PROTECT AF Baseline Risk Factors

Characteristic	Device N=463	Control N=244	P-value
$CHADS_2$ Score			0.411
1	156/463 (33.7%)	66/244 (27.0%)	
2	158/463 (34.1%)	88/244 (36.1%)	
3	89/463 (19.2%)	51/244 (20.9%)	
4	37/463 (8.0%)	24/244 (9.8%)	
5	19/463 (4.1%)	10/244 (4.1%)	
6	4/463 (0.9%)	5/244 (2.0%)	
$CHADS_2$ Score (Continuous)	2.2 ± 1.2 (463) (1.0, 6.0)	2.3 ± 1.2 (244) (1.0, 6.0)	0.072
$CHADS_2$ Risk Factors			
CHF	124/463 (26.8%)	66/244 (27.0%)	0.9392
Hypertension	415/463 (89.6%)	220/244 (90.2%)	0.8243
Age ≥ 75	190/463 (41.0%)	115/244 (47.1%)	0.1198
Diabetes	113/463 (24.4%)	72/244 (29.5%)	0.1423
Stroke/TIA	82/463 (17.7%)	49/244 (20.1%)	0.4404
CHA_2DS_2-VASc Score			0.469
1	44/460 (9.6%)	16/239 (6.7%)	
2	105/460 (22.8%)	54/239 (22.6%)	
3	139/460 (30.2%)	64/239 (26.8%)	
4	91/460 (19.8%)	47/239 (19.7%)	
5	45/460 (9.8%)	32/239 (13.4%)	
6	27/460 (5.9%)	19/239 (7.9%)	
7	5/460 (1.1%)	5/239 (2.1%)	
8	2/460 (0.4%)	2/239 (0.8%)	
9	0/460 (0.0%)	0/239 (0.0%)	
CHA_2DS_2-VASc Score (Continuous)	3.2 ± 1.4 (460)	3.5 ± 1.5 (239)	0.022

Primary Effectiveness Endpoint

The sponsor conducted the primary effectiveness analysis on the ITT population for two sets of data: a 600 patient-year dataset and 900 patient-year dataset. The 600 patient-year data was submitted as the primary dataset as specified in the statistical plan and the sponsor subsequently updated this dataset with the 900 patient-year cohort. For the 600 patient-year dataset, the 95% credible interval for the relative risk (rate ratio) was lower than the non-inferiority margin of 2.0. For the 900 patient-year dataset, the 95% credible interval for the relative risk (rate ratio) was also lower than the non-inferiority margin of 2.0. For both datasets, the posterior probability of non-inferiority exceeded the pre-specified non-inferiority criterion of 0.975 (non-inferiority met, Table 64). However, the criterion for WATCHMAN superiority vs. warfarin was not met.

Table 64: PROTECT AF Primary Effectiveness Endpoint Results (ITT)

Analysis Cohort	Device		Control		Relative Risk (95% CrI)		Posterior Probabilities	
	Rate (95% CrI)		Rate (95% CrI)				Non-inferiority	Superiority
600 pt-yrs	4.4	(2.6, 6.7)	5.8	(3.0, 9.1)	0.76	(0.39, 1.67)	0.992	0.734
900 pt-yrs	3.4	(2.1, 5.2)	5.0	(2.8, 7.6)	0.68	(0.37, 1.41)	0.998	0.837

Pt-yrs = patient-years CrI = credible interval
Rate = event rate per 100 patient-years (calculated as 100*N events/Total patient-years) Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate

The events contributing to the primary effectiveness endpoint are shown by type for the 600 pt-yr and 900 pt-yr datasets in Tables 65 and 66, respectively.

Table 65: Events Contributing to Primary Effectiveness Endpoint (600 pt-yrs ITT)

	Device		Control	
Type	N Events	% of Randomized Subjects	N Events	% of Randomized Subjects
Stroke - Ischemic	13	2.9%	4	1.7%
Death – Cardiovascular and Unexplained	2	0.4%	5	2.1%
Stroke - Hemorrhagic	1	0.2%	4	1.7%
Systemic Embolization	2	0.4%	0	0.0%

Table 66: Events Contributing to Primary Effectiveness Endpoint (900 pt-yrs ITT)

	Device		Control	
Type	N Events	% of Randomized Subjects	N Events	% of Randomized Subjects
Stroke - Ischemic	14	3.0%	5	2.0%
Death – Cardiovascular and Unexplained	3	0.6%	5	2.0%
Stroke - Hemorrhagic	1	0.2%	6	2.5%
Systemic Embolization	2	0.4%	0	0.0%

Primary Safety Endpoint

The sponsor also conducted the primary safety analysis on the ITT Population for both the 600 pt-yr and 900 pt-yr datasets. For the 600 patient-year dataset, the primary safety event rate was 11.6% for the device group and 4.1% for the control group. For the 900 patient-year dataset, the primary safety event rate was 11.6% for the device group and 4.1% for the control group (Table 67). There was no pre-specified hypothesis for the safety endpoint.

Table 67: Events Contributing to Primary Effectiveness Endpoint (900 pt-yrs ITT)

Data Set	Device			Control			Rel. Risk (95% CrI)
	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	N Subjects	N Events/ Total Pt-Yrs	Rate (95% CrI)	
600 pt-yrs	454	45/386.4	11.6 (8.5, 15.3)	238	9/220.4	4.1 (1.9, 7.2)	2.85 (1.48, 6.42)
900 pt-yrs	463	48/554.2	8.7 (6.4, 11.3)	244	13/312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)

The events contributing to the primary safety endpoint are shown by type for the 600 pt-yr and 900 pt-yr datasets in Tables 68 and 69, respectively.

Table 68: Events Contributing to Primary Safety Endpoint 600 pt-yrs (ITT)

	Device		Control	
Type	N Events	% of Randomized Subjects	N Events	% of Randomized Subjects
Pericardial Effusion – Serious*	23	5.1%	0	0.0%
Gastrointestinal Bleeding	9	2.0%	4	1.7%
Stroke - Ischemic	5	1.1%	0	0.0%
Stroke - Hemorrhagic	1	0.2%	4	1.7%
Device Embolization	3	0.7%	0	0.0%
Esophageal Tear	1	0.2%	0	0.0%
Cranial Bleed	1	0.2%	0	0.0%
Major Bleed Requiring Transfusion	1	0.2%	0	0.0%
Arrhythmias	1	0.2%	0	0.0%
Anemia Requiring Transfusion	0	0.0%	1	0.4%

* Serious pericardial effusion was defined as one that required either pericardiocentesis or surgery.

Table 69: Events Contributing to Primary Safety Endpoint 900 pt-yrs (ITT)

	Device		Control	
Type	**N Events**	**% of Randomized Subjects**	**N Events**	**% of Randomized Subjects**
Pericardial Effusion – Serious*	22	4.8%	0	0.0%
Gastrointestinal Bleeding	10	2.2%	6	2.5%
Stroke - Ischemic	5	1.1%	0	0.0%
Stroke - Hemorrhagic	1	0.2%	6	2.5%
Device Embolization	3	0.7%	0	0.0%
Esophageal Tear	1	0.2%	0	0.0%
Cranial Bleed	2	0.4%	0	0.0%
Major Bleed Requiring Transfusion	2	0.4%	0	0.0%
Arrhythmias	1	0.2%	0	0.0%
Bruising – Hematoma	1	0.2%	0	0.0%
Anemia Requiring Transfusion	0	0.0%	1	0.4%

* Serious pericardial effusion was defined as one that required either pericardiocentesis or surgery.
** Subdural hematoma was reported as cranial bleed.

Appendix B – What is Bayesian Statistics?

Bayesian statistics is an approach for learning from evidence as it accumulates. The Bayesian approach uses Bayes' Theorem to combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

When good prior information on clinical use of a device exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial. However, the Bayesian approach is useful even in the absence of prior information. For example, the approach can accommodate adaptive trials (e.g., interim analyses or change to sample size) and even some unplanned, but necessary trial modifications. Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making.

Prior Distribution

As an illustration, suppose that the Greek letter **θ** represents a parameter in a clinical trial. The initial knowledge about **θ** prior to data collection is represented by the prior distribution for **θ**, which we denote in symbols as P(**θ**). Suppose **θ** is the rate of a serious adverse event. Its possible values lie between 0 and 1. The prior distribution might give preference to lower values of **θ** (see Figure 13). The probability that **θ** takes on any particular set of values is determined by the area under the curve for those values. So the prior probability that the adverse event rate **θ** is greater than 0.4 (the shaded area) is about 0.38.

An *informative* prior distribution gives preferences to some values of the quantity of interest as being more likely than others (See Figure 13). Lack of preference among the values or lack of information can be represented through a *non-informative* prior distribution (e.g., a uniform prior which indicates no preference for any value of **θ**).

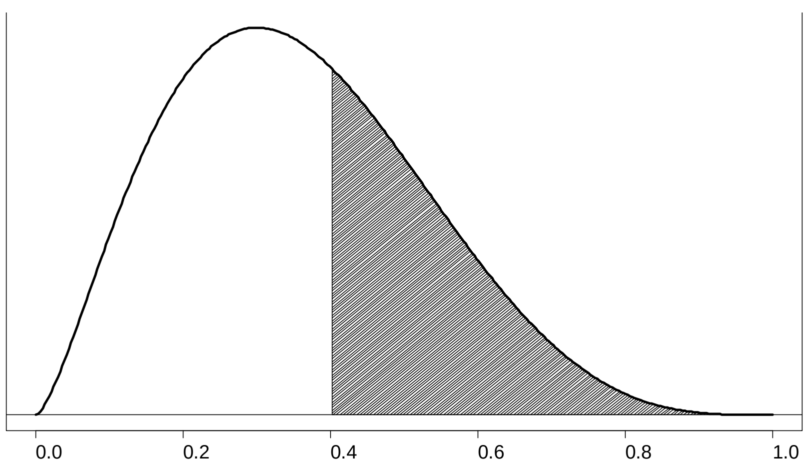


Figure 13. Example of a unimodal, right-skewed prior distribution for a serious adverse event rate, denoted by θ. The prior probability that θ is greater than 0.4 (the shaded area) is about 0.38.

Likelihood of the Observed Data

Now suppose outcomes have been obtained from a clinical trial. The likelihood function is a mathematical representation of the relationships between observed outcomes and the parameter **θ**. The likelihood function can be expressed in symbols by P(data |**θ**), which is the conditional probability of observing the data given a specific value of the parameter **θ**, for each possible value of **θ**.

Posterior Distribution

The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter **θ** conditional on the observed data, which can be denoted in symbols as P(**θ**| data). Bayes' theorem is used to update the prior distribution for **θ,** P(**θ**), via the likelihood, P(data|**θ**), to obtain the posterior distribution for **θ**, P(**θ**|data). At the conclusion of the trial, the information about **θ** is summarized by this posterior distribution, and Bayesian inferences are based on it.

As an example, Figure 14 shows the posterior distribution that would be obtained if we started with the prior shown in Figure 13 and observed data with 1 adverse event in 10 patients. Since the adverse event rate observed in these patients is 0.10, the distribution has shifted further to the left (that is, it now favors even lower values for **θ**). The posterior probability that **θ** is greater than 0.4 (the shaded area) is about 0.04. The probability that the adverse event rate is greater than 0.4 has been reduced from about 0.38 (the prior probability) to about 0.04 (the posterior probability) by the favorable trial results.

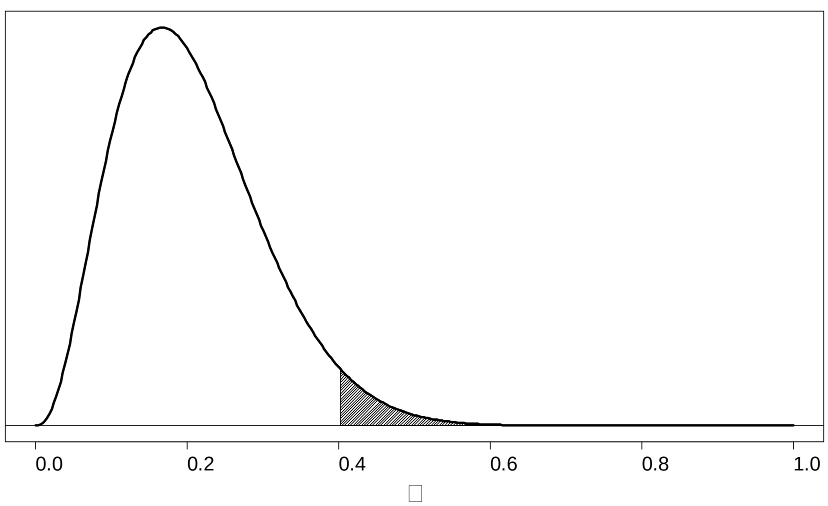


Figure 14. Example of a unimodal, right-skewed posterior distribution for a serious adverse event rate, denoted by θ, after observing one adverse event in 10 patients and updating the prior probability in Figure 1. The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04.

The posterior distribution that has been obtained today may serve as a prior distribution when more data are gathered. The more information that is accrued, the less uncertainty there may be about the posterior distribution for **θ**. If enough data are collected, the relative importance of the prior distribution will be negligible compared to the likelihood.

Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.

A pre-specified decision rule is used to demonstrate hypotheses that define safety and effectiveness with reasonable assurance. For Bayesian trials, one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if its posterior probability is large enough (e.g., 95 or 99 percent).

Predictive Distribution

The Bayesian approach allows for the derivation of a special type of posterior probability; namely, the probability of unobserved outcomes (future or missing) given what has already been observed. This probability is called the *predictive probability*. Collectively, the probabilities for all possible values of the unobserved outcome are called the predictive distribution. Predictive distributions have many uses, including determining when to stop a trial (based on predicting outcomes for patients not yet observed) or adjusting trial results for missing data (imputation).

These uses are discussed in more detail below in **Analyzing a Bayesian Clinical Trial**.

Exchangeability

Exchangeability is a fundamental concept underlying statistical inference. It can be of particular importance in Bayesian trials. Formally, we would say that units (patients or trials) are considered *exchangeable* if the probability of observing any particular set of observations on those units is invariant to any re-ordering of the units.

- **Exchangeability of patients**

  In a clinical trial, patients within the trial are usually assumed to be exchangeable. Under exchangeability, patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other re-indexing or re-numbering of the patients. If patients in the trial are exchangeable with patients in the population from which they were sampled (e.g., the intended use population), then inferences can be made about the population on the basis of data observed on the trial patients. Thus, the concept of a *representative sample* can be expressed in terms of exchangeability.

- **Exchangeability of trials**

  For a Bayesian clinical trial, another level of exchangeability might be assumed. Namely, the trial can be assumed to be exchangeable with other previous trials when the previous trials are considered to be good prior information. The assumption of trial exchangeability enables the current trial to “borrow strength” from the previous trials, while acknowledging that the trials are not identical in all respects. Thus, exchangeability is important in the development of realistic models for combining trial data with prior information.

Bayesian Adaptive Designs

Adaptive designs use accumulating data to decide how to modify certain aspects of a trial according to a pre-specified plan without undermining the validity and integrity of the trial.

Adaptive trial designs have the potential to provide optimal statistical inference and to improve quality, speed and efficiency of decision making.

An adaptive Bayesian clinical trial can involve interim looks to adapt the sample size (to stop or to continue patient accrual) or interim looks for the purpose of possibly stopping the trial early either for success, futility, or harm.

A purely Bayesian approach would allow for continuous design adaptation as the trial take place. However, in order to maintain the integrity of the trial while minimizing operational biases, the Bayesian adaptive trial should be adaptive *by design*.

Analyzing a Bayesian Clinical Trial

The results, conclusions, and interpretation of a Bayesian analysis all rely on the posterior distribution. Consequently, results and conclusions for a Bayesian trial are based only on the posterior distribution.

Hypothesis testing

For Bayesian hypothesis testing, one can use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.

Interval estimation

Bayesian interval estimates are based on the posterior distribution and are called *credible intervals*. If the posterior probability that an endpoint lies in an interval is 0.95, then this interval is called a 95 percent *credible interval*.

Predictive probabilities

Uses of predictive probabilities include the following:

Deciding when to stop a trial

One can use a predictive probability at an interim point as the rule for stopping the trial. If the predictive probability that the trial will be successful is sufficiently high (based on results at the interim point), the trial may be stopped and declared successful.

Exchangeability is a key issue here: these predictions are reasonable only if you can assume the patients who have not been observed are exchangeable with the patients who have. This assumption is difficult to formally evaluate but may be more plausible in some instances (e.g., administrative censoring) than others (e.g., high patient drop-out).

Predicting outcomes for future patients

One may also calculate the predictive probability of the outcome of a future patient, given the observed outcomes of the patients in a clinical trial, provided the current patient is exchangeable with the patients in the trial.

Predicting (imputing) missing data

One may use predictive probabilities to predict (or *impute*) missing data, and trial results can be adjusted accordingly. The adjustment depends on the assumption that patients with missing outcomes follow the same statistical model as patients with observed outcomes. This means the missing patients are exchangeable with the non-missing patients, or that data are *missing at random*.

Predicting a clinical outcome from earlier measurements

If patients have measurements of the same outcome at earlier and later follow-up visits, one can make predictions for the later follow-up visit (even before the follow-up time has elapsed).

Interim analyses

Bayesian interim analyses typically involve the following applications:

Applying posterior probability

One method stops the trial early if the posterior probability of a hypothesis at the interim look is large enough. In other words, the same Bayesian hypothesis test is repeated during the course of the trial.

Applying predictive distribution

Another method calculates at interim stages the probability that the hypothesis test will be successful at the end of accrual and follow-up. This method uses the Bayesian predictive distribution for patients yet to be measured. If the predictive probability of success is sufficiently high, the trial may stop early. If the predictive probability is very low, the trial may stop early for futility.

Appendix C – The Bayesian approach in the PREVAIL trial

C1. The first and second primary endpoints

- **The model**

The following piecewise exponential model was pre-specified as the model for the event rates for the first and second primary endpoints:

$$\lambda_{G,Z,T}(t) = \begin{cases} \lambda_{G,Z,1} & 0 < t \leq 7 \\ \lambda_{G,Z,2} & 7 < t \leq 60 \\ \lambda_{G,Z,3} & 60 < t \leq 182 \\ \lambda_{G,Z,4} & 182 < t \end{cases} \tag{1}$$

where t is measured in days, $G \in \{D,C\}$ where D represents the device group and C represents the control group, and $Z \in \{1,2\}$ where Z=1 for cardiovascular/unexplained death and hemorrhagic stroke and Z=2 for ischemic stroke and systemic embolism.

The model-based 18-month rate of any event for group G is the probability of any event (Z = 1 or 2) occurring within 18 months in group G calculated as follows

$$\begin{aligned} r_{G,A} &= \Pr(\text{Any Event by 18 months in Group } G) = \\ &1 - \exp\left(-\left(7(\lambda_{G,1,1} + \lambda_{G,2,1}) + 53(\lambda_{G,1,2} + \lambda_{G,2,2}) + 122(\lambda_{G,1,3} + \lambda_{G,2,3}) + 365(\lambda_{G,1,4} + \lambda_{G,2,4})\right)\right) \end{aligned} \tag{2}$$

The model-based 18-month rate of thrombotic event for group G is the probability of an event of type Z=2 occurring within 18 months (excluding the first 7 days) for group G calculated as follows

$$\begin{aligned} r_{G,T} &= \Pr(\text{Thrombolic Event by 18 months in Group} G) = \\ &1 - \exp\left(-(53\lambda_{G,2,2} + 122\lambda_{G,2,3} + 365\lambda_{G,2,4})\right) \end{aligned} \tag{3}$$

- **Prior distributions**

Historical priors for each interval in the piecewise exponential model were based on the dataset from the previous PROTECT AF trial that included 1588 patient year follow-up (locked on April 14, 2010). This data was discounted 50%. For each event rate $\lambda_{G,Z,,T}$, for group G, event type Z and time period T the prior distribution is of the form

$$\lambda_{G,Z,T} \sim \text{Gamma}(\alpha^0_{G,Z,T}, \beta^0_{G,T}). \tag{4}$$

where $\alpha^0_{G,Z,T}$ = one-half the events of type Z observed in time period T in group G from the PROTECT AF study and $\beta^0_{G,T}$ = one-half the exposure time in days observed in time period T in group G from the PROTECT AF study. If there were no events, the value of $\alpha^0_{G,Z,T} = 0.001$ was substituted for 0 to ensure a proper posterior distribution.

- **Posterior distributions**

After observing $Ev_{G,Z,T}$ total events of type Z in group G within period T and with total patient exposure time $Expos_{G,T}$ in group G within period T in the PREVAIL study, the posteriors are

$$[\lambda_{G,Z,T} \mid Ev_{G,Z,T}, Expos_{G,T}] \sim \text{Gamma}\,(\alpha_{G,Z,T} = \alpha^0_{G,Z,T} + Ev_{G,Z,T}, \beta_{G,T} = \beta^0_{G,T} + Expos_{G,T}) \quad (5)$$

Patient exposure was to be calculated from the date of randomization (for ITT analysis) to the first appropriate event or censoring date (last follow-up date for subjects without an event) for each subject and aggregated over the analysis population. Subjects without an event and who exited the study (had an End of Study case report form completed) were to have the censoring date equal to the date of study exit.

- **Final analysis**

The final analyses were performed 6 months after the last patient was enrolled as pre-specified in the statistical analysis plan (SAP).

The posterior distributions for the event rates $\lambda_{G,Z,T}$ were calculated for each event type (Z=1,2), treatment group (G=D,C) and time period (T=1,2,3,4) according to equation (5). Then, the posterior distribution for the 18-month event rates for any event, $r_{G,A}$, for the device and control groups were calculated according to equation (2) along with the posterior distribution for the risk ratio $rr_A = r_{D,A} / r_{C,A}$. Also, the posterior distribution for the 18-month event rates for thrombotic events sans the first seven days, $r_{G,T}$, for the device and control groups were calculated according to equation (3) along with the posterior distributions for the risk ratio $rr_T = r_{D,T} / r_{C,T}$ and risk difference, $rd_T = r_{D,T} - r_{C,T}$.

C2. The third primary endpoint

A Bayesian method based on a conjugate beta-binomial model was used to incorporate the previously collected data from PROTECT AF and the CAP Registry through a prior distribution in estimating the event rate for the third primary endpoint. No discounting weight was applied to the prior, so this was essentially direct data pooling.

- **Prior distribution**

Data for the prior is based on the PROTECT AF 1588 patient year data set (locked on April 14, 2010) and the CAP Registry data set (locked on May 12, 2010). There were 734 patients in PROTECT AF and CAP who would be eligible for the new study based on their risk factors and 13 events in these patients yielding an observed percentage of patients with events of 1.8%. These results were applied via a Beta(13,721) distribution, a conjugate prior to the binomial distribution that models the third primary endpoint in the PREVAIL trial.

- **Posterior distribution**

Given E new events in N total patients from PREVAIL trial, the posterior distribution for the event rate corresponding to the third primary endpoint is Beta(13 + E, 721 + N – E).

C2. The validity of model assumptions

- **Exchangeability of prior and PREVAIL trials**

The exchangeability assumption between PROTECT AF and PREVAIL studies appeared to be of concern in terms of study design and conduct. In particular, treatment effect in PROTECT AF study was significantly confounded with warfarin and antiplatelet therapy use. This concern appeared not to affect the third primary endpoint Bayesian analysis since it is measured on a short follow-up time post-procedure. Therefore, the prior data was discounted 50% in the analyses for the first and second primary endpoints only. The discounting weight was prospectively agreed to by both FDA and the sponsor.

- **Assumption of constant hazard rate in the piecewise exponential model**

Rates by 60 day intervals for the first primary endpoint are displayed in Figure 13 with 95% confidence intervals based on Poisson distribution calculations. The sponsor notes that “For each of the randomized groups, for each interval with observed events, the width of the confidence interval exceeds the differences between the point estimates for the rates.” The sponsor concludes that “These results are consistent with the study design assumptions.” FDA performed analyses of the constant hazard rate assumption for 60 and 90 day intervals within the time period of 183-547 days, over which the model assumes a constant hazard rate. The results of these analyses are shown in Figures 14 (60 day intervals) and 15 (90 day intervals). In both cases, the tests of homogeneity of Poisson rates show no statistically significant p-values, thus failing to reject the null hypothesis of homogeneity of the rates.

Figure 15: Sponsor’s analysis of hazard rates by 60 day intervals

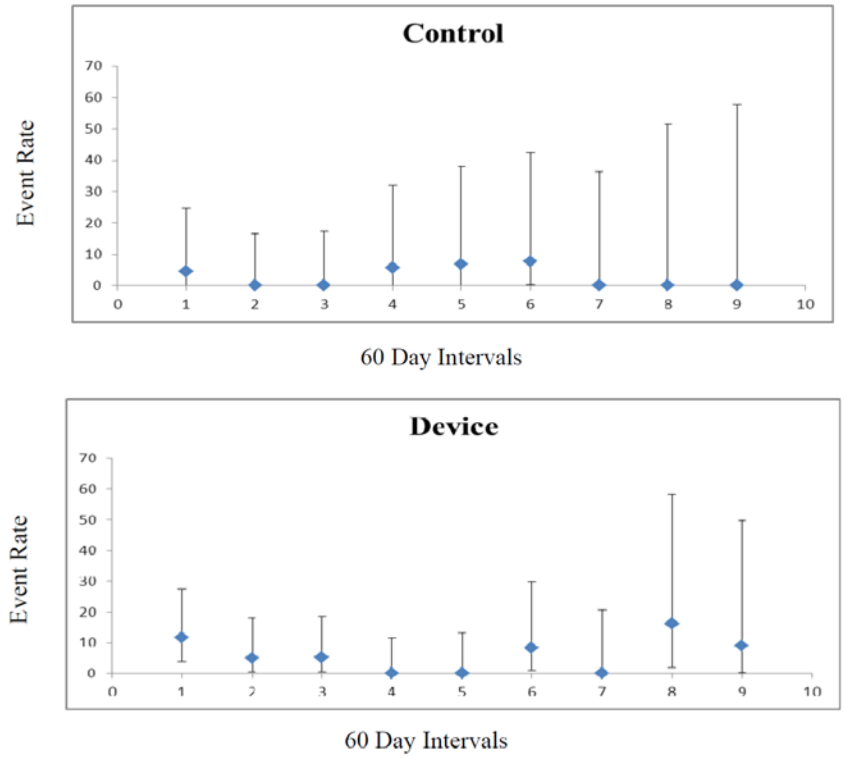
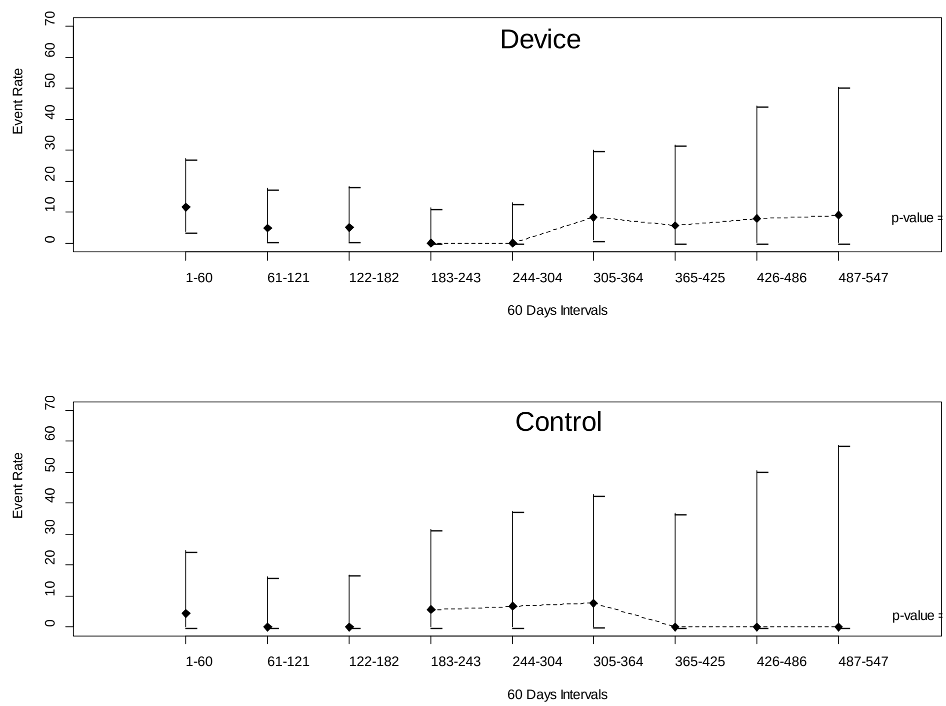
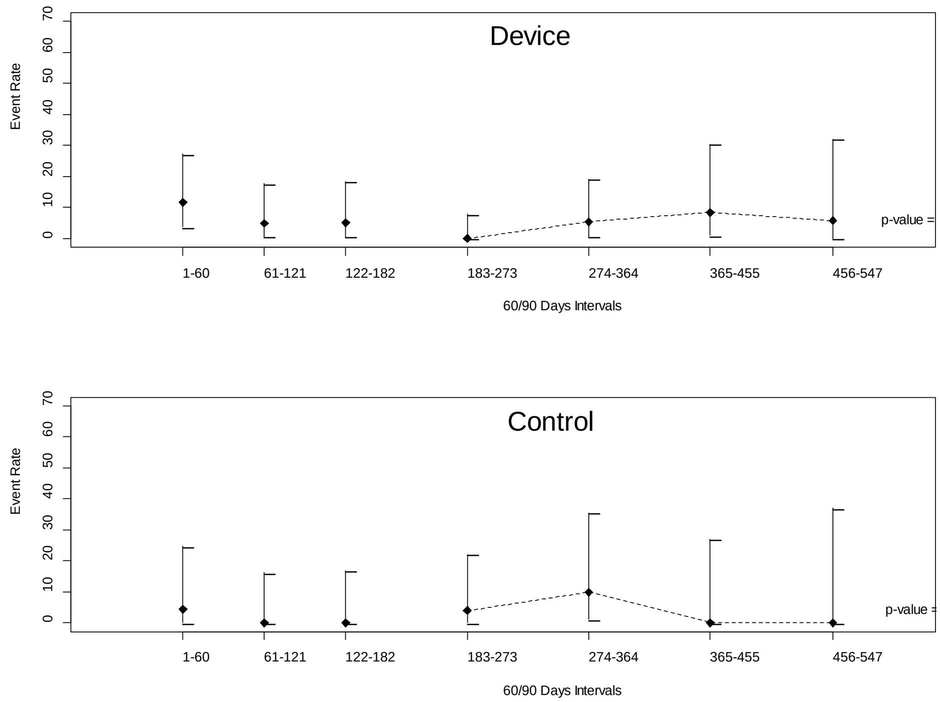


Figure 16: FDA's analysis of hazard rates by 60 day intervals



The p-values correspond to tests of homogeneity of the Poisson rates across 60 days interval strata within time period 183-547 days.

Figure 17: FDA's analysis of hazard rates by 90 day intervals



The p-values correspond to tests of homogeneity of the Poisson rates across 90 days interval strata within time period 183-547 days.

Appendix D – Key Definitions

Adverse event (AE): At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any undesirable clinical occurrence in a subject. Adverse events will be categorized as mild, moderate and severe/serious.

Serious Adverse Event (SAE): Any untoward medical occurrence that is any Adverse Event that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, the WATCHMAN device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with the WATCHMAN device that relates to the rights, safety, or welfare of subjects.

Arrhythmias: An alteration in rhythm of the heartbeat that requires treatment with a device or anti-arrhythmic medication.

Atrial Fibrillation:

Lone Atrial Fibrillation: Atrial fibrillation in a structurally normal heart not caused by an underlying heart disease.

Non-valvular Atrial Fibrillation: Atrial fibrillation in the absence of rheumatic mitral valvular heart disease.

Paroxysmal Atrial Fibrillation: An intermittent form of atrial fibrillation that is characterized by a sudden onset and abrupt cessation of this rhythm. Spontaneous termination may occur in < 7 days and most often in < 48 hours. Medical documentation is required.

Persistent Atrial Fibrillation: Atrial fibrillation that is not self-terminating, lasting > 2 days, and termination using pharmacologic therapy or electrical cardioversion may be required. Persistent AF may be the first presentation of the arrhythmia or may be preceded by recurrent episodes of paroxysmal AF.

Permanent Atrial Fibrillation: Atrial fibrillation that has been present for at least 2 days and fails to terminate using cardioversion, or is terminated but relapses within 24 hours.

Bleeding Complication: Rectal bleeding, hematuria, epistaxis, bleeding from varicose veins, oral bleeding and prolonged bleeding from a laceration, bruising-hematoma, hemothorax, red eye and thrombosis.

Cardiac perforation (myocardial perforation): A Cardiac Perforation is an effusion >1cm that causes hemodynamic change which requires intervention and/or closure of the hole by surgical intervention and is classified as a SERIOUS ADVERSE EVENT/Safety endpoint.

Cardiac tamponade: A cardiac tamponade is a pericardial effusion that requires drainage and classified as a SERIOUS ADVERSE EVENT/Safety endpoint.

$CHADS_2$ scale: A classification scheme to stratify patients by their risk of future stroke. A patient is assigned a score from 1 to 6 based on the following factors:

1 point for each of:

- Recent CHF
- History of Hypertension
- Age at least 75 years
- Diabetes

2 points for having had a prior stroke or TIA

Death: Deaths will be recorded on a patient data form with a detailed description of the circumstances surrounding the patient's death documented. Autopsy results and explanation of the device will be obtained whenever possible. Deaths will also be sub-categorized as peri-procedural(<30days of procedure) and late-term (>31 days after the procedure)

Device Failure: A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

Device Malfunction: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

Device Erosion: Device erosion is tissue wear resulting from mechanical loading as evidenced by device protrusion.

Device Embolization: An obstruction or occlusion by a device that has been dislodged from the LAA and is introduced into the circulatory system potentially occluding vessels and / or organs by occluding its blood supply.

Excessive anticoagulation event: Any INR>4.0mg will constitute an excessive anticoagulation event as described in the warfarin package insert.

INR Therapeutic range: 2.0-3.0.

Pericardial effusion (hemodynamically insignificant): A Pericardial Effusion is increased fluid within the pericardial sac that does not cause circulatory compromise and does not require drainage. It will be classified as NON-SERIOUS ADVERSE EVENT / not a safety endpoint unless it requires prolonged hospitalization and/or progresses to tamponade or perforation requiring intervention or transfusion.

Stroke

Ischemic Stroke: Sudden onset of a focal neurological deficit with symptoms and/or signs
persisting more than 24 hours or symptoms less than 24 hours confirmed by CT or MRI, including a full neurological exam by a Neurologist.

Hemorrhagic Stroke: Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage, including full neurological exam by a Neurologist.

Systemic Embolism: Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation).
In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

Transient ischemic attack (TIA): Acute focal neurological event (including focal motor deficit aphasia, difficulty walking, hemi sensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes and up to 24 hours that is MR imaging negative, including full neurological exam by a Neurologist. All TIAs will be adjudicated for seriousness and causality by the CEC.